

Exhibit 43

In The Matter Of:
Anastasia Brower, et al. v.
Johnson & Johnson, Inc., et al.

Michael Birrer, M.D.
September 25, 2018

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Page 1

1 IN THE STATE COURT OF FULTON COUNTY

2 STATE OF GEORGIA

3 ANASTASIA BROWER, a minor,
 4 through her legal guardian
 5 PAMELA RUSSELL, and
 Estate of DIANE BROWER,
 deceased,

6 Plaintiffs,

7 vs. CASE NO. 16-EV-005534

8 JOHNSON & JOHNSON, INC.,
 9 JOHNSON & JOHNSON CONSUMER
 COMPANIES, INC., and
 10 IMERYS TALC AMERICA, INC.,
 Defendants.

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16 The deposition of MICHAEL BIRRER,
 17 M.D., was taken before Greta H. Duckett,
 18 Certified Court Reporter, Registered
 19 Professional Reporter, and Certified Realtime
 20 Reporter, as Commissioner, on Tuesday,
 21 September 25, 2018, commencing at
 22 approximately 8:47 a.m., at 1700 Sixth Avenue
 23 South, Birmingham, Alabama.

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4 APPEARANCES

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2 I N D E X

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 13 Materials for Dr. Michael
 Birrer

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1 MICHAEL BIRRER, M.D.,

2 the witness, having first been duly

3 sworn to speak the truth, the whole truth and

4 nothing but the truth, testified as follows:

5 EXAMINATION

6 BY MR. DEARING:

7 Q. Good morning, Doctor. My name

8 is David Dearing, and I represent Ms. Brower

9 and her family. I'm just going to ask you

10 some questions. You've been disclosed to us

11 as an expert witness, potentially, to be

12 called at trial. I'm going to ask you just

13 some questions in your capacity as that

14 witness.

15 Since we have not received a

16 report from you, I'm probably going to have

17 to start from the very beginning and sort of

18 work my way to where I would normally start

19 if we had a report. So some of the questions

20 may seem elementary, but I just haven't met

21 you before. Anyway, I apologize for starting

22 so far in the beginning.

23 MS. AHERN: I just want to put

<p style="text-align: right;">Page 5</p> <p>1 on the record that you do have a</p> <p>2 prior report of his that expresses</p> <p>3 general opinions in the same issues</p> <p>4 that he'll be testifying to today</p> <p>5 and that we have an agreement that</p> <p>6 this will be a case-specific</p> <p>7 deposition and that you can't cover</p> <p>8 new materials that he has reviewed</p> <p>9 or relied on since his prior</p> <p>10 deposition. But I just wanted to</p> <p>11 make sure that was on the record.</p> <p>12 MR. DEARING: Okay. And are</p> <p>13 you referring to the deposition</p> <p>14 from Swann that Russ Abney took?</p> <p>15 MS. AHERN: The 12-hour</p> <p>16 deposition. Yes.</p> <p>17 MR. DEARING: Okay. I wasn't</p> <p>18 there. I've never taken a 12-hour</p> <p>19 deposition in my life. I don't</p> <p>20 know 12 hours of gynecologic</p> <p>21 oncology.</p> <p>22 BY MR. DEARING:</p> <p>23 Q. First of all, would you state</p>	<p style="text-align: right;">Page 7</p> <p>1 is gynecologic oncology patients.</p> <p>2 Q. Do you have a particular focus</p> <p>3 within the gynecologic oncology realm?</p> <p>4 A. Essentially, 95 percent of the</p> <p>5 patients are ovarian cancer.</p> <p>6 Q. How long have you been in the</p> <p>7 position of director of the cancer center?</p> <p>8 A. It's about a year and two</p> <p>9 months now.</p> <p>10 Q. Were you here in some other</p> <p>11 capacity, or did you come from another</p> <p>12 facility?</p> <p>13 A. I came from Harvard Medical</p> <p>14 School and Mass. General.</p> <p>15 Q. Did you work with Dr. William</p> <p>16 Welch in Massachusetts?</p> <p>17 A. Dr. Welch was over at the</p> <p>18 Brigham as a pathologist. I was at the</p> <p>19 Mass. General. So we would cross paths at</p> <p>20 some of the conferences.</p> <p>21 Q. I think you've published</p> <p>22 together, right?</p> <p>23 A. It's likely I'm on some papers</p>
<p style="text-align: right;">Page 6</p> <p>1 your name, please.</p> <p>2 A. Michael Birrer.</p> <p>3 Q. What is your profession?</p> <p>4 A. I'm trained as a medical</p> <p>5 oncologist and physician scientist.</p> <p>6 Q. What is your title here at UAB?</p> <p>7 A. Director of the UAB</p> <p>8 Comprehensive Cancer Center.</p> <p>9 Q. Can you tell me just generally</p> <p>10 what that encompasses? It sounds</p> <p>11 administrative.</p> <p>12 A. Well, I run the cancer center.</p> <p>13 So it has an administrative component, and it</p> <p>14 extends over the entire operation of the</p> <p>15 cancer center. So it's all of the disease</p> <p>16 centers, clinical trials, the research</p> <p>17 component. And then, in this particular job,</p> <p>18 we are also creating a cancer service center,</p> <p>19 which means I'll be responsible for the</p> <p>20 clinical component of the way cancer care is</p> <p>21 delivered in the hospital.</p> <p>22 As part of my negotiated job, I</p> <p>23 still see patients half a day a week, which</p>	<p style="text-align: right;">Page 8</p> <p>1 from Dr. Mock where Dr. Welch would be on</p> <p>2 those.</p> <p>3 Q. What about John Godleski,</p> <p>4 pathology at Brigham?</p> <p>5 A. Never really crossed paths with</p> <p>6 him, and I don't think I'm on any papers with</p> <p>7 him.</p> <p>8 Q. What about Dan Cramer, the</p> <p>9 epidemiologist?</p> <p>10 A. So we would cross paths, again,</p> <p>11 at conferences. We worked a little bit on</p> <p>12 early -- the Early Detection Research Network</p> <p>13 grant and probably on a couple of papers,</p> <p>14 again, from Dr. Mock, where Dan Cramer would</p> <p>15 be on it and I would be on it.</p> <p>16 Q. That was my next question.</p> <p>17 Have you published with Dr. Cramer?</p> <p>18 A. Yeah.</p> <p>19 Q. What about Dr. Harlow over</p> <p>20 at Harvard and --</p> <p>21 A. Ed Harlow?</p> <p>22 Q. Yes.</p> <p>23 A. No.</p>

<p style="text-align: right;">Page 9</p> <p>1 Q. You haven't worked with him or 2 published with him? 3 A. I don't believe so, no. 4 Q. What did you do to prepare for 5 this deposition today? 6 A. Well, it was similar to the 7 previous deposition. I reviewed, you know, 8 the -- some of the literature in relationship 9 to the epidemiologic studies for talc, the 10 biologic evidence, IARC reports. 11 Q. So you've reviewed those 12 recently in preparation for this deposition 13 or just -- 14 A. Previously, and then would have 15 highlighted them again for this one. 16 Q. And you've been offered as an 17 expert by Johnson & Johnson. Have you met 18 with Johnson & Johnson lawyers to prepare for 19 this deposition? 20 A. So Hunter and I met together 21 three times. 22 Q. Okay. Just to prepare for this 23 deposition?</p>	<p style="text-align: right;">Page 11</p> <p>1 deposition that's not on that reliance list? 2 MS. AHERN: Objection to form. 3 A. It's pretty inclusive. I did 4 review my own report. 5 Q. Okay. Is that listed on here? 6 I can't remember. 7 A. I didn't see it. So -- 8 Q. I've reviewed your old report 9 too, so I'll try not to retread that ground. 10 I did want to ask you some questions to 11 clarify some things, and I'll get to that in 12 a while. 13 Also, before I forget, I did 14 not bring a copy of your CV. But as we 15 discussed before we went on the record, a 16 copy of your CV was provided with our 17 notice -- or disclosure of your name as an 18 expert. To your knowledge, is that the most 19 current, recent CV? 20 A. Yes. 21 Q. All right. 22 A. 6/28, I think. 23 Q. Have you ever testified at</p>
<p style="text-align: right;">Page 10</p> <p>1 A. Correct. 2 Q. Can you just give me an idea 3 how much total time you spent with Ms. Ahern? 4 A. This time? 5 Q. For this deposition. 6 A. About five hours. 7 (Exhibit #1 was marked for 8 identification.) 9 BY MR. DEARING: 10 Q. I was provided a document which 11 I believe lists your reliance materials for 12 this case, and we've marked it as Exhibit #1. 13 Would you take a look at that and tell me if 14 that accurately reflects the reliance 15 materials that you have reviewed and relied 16 on for this deposition? 17 A. It looks pretty inclusive. 18 Obviously, a lot of the papers were related 19 to the previous deposition. I might have 20 just looked at them briefly. But the newer 21 ones, I've looked at more closely. 22 Q. Okay. Can you think of 23 anything that you may have relied on for this</p>	<p style="text-align: right;">Page 12</p> <p>1 trial? 2 A. I testified in a malpractice 3 case in Maine. That's a three-judge panel. 4 Q. I read about that in your 5 previous deposition. 6 A. In 2012, yes. 7 Q. You have never testified in a 8 jury trial before? 9 A. Correct. 10 Q. And this would be the second 11 time you've been deposed in this talcum 12 powder litigation, is that right? 13 A. Correct. 14 Q. And the last time you were 15 deposed was when Mr. Abney took your 16 deposition in the Swann case? 17 A. June 2017, I believe, yeah. 18 Q. So you've been offered as an 19 expert in the field of gynecologic oncology. 20 Are there any other particular fields that 21 you feel qualified as an expert in? 22 MS. AHERN: Objection to form. 23 A. Well, I think that from a</p>

<p style="text-align: right;">Page 13</p> <p>1 clinical standpoint, I would say my area of 2 expertise is gynecologic cancers. From a 3 laboratory standpoint, there's a lot of 4 experience on genomics of cancer, biologic 5 processes of transformation, and a lot of 6 that work is focused on ovarian cancer. 7 Q. I read, possibly in your 8 report -- it might have been in your 9 deposition -- that the majority of your 10 research has been in genomic biology. Is 11 that a fair statement? 12 MS. AHERN: Objection to form. 13 A. A lot of it is -- I would call 14 it molecular biology, yeah. 15 Q. Clearly, you have a focus in 16 genetics or genome research. Would you say 17 that that makes up the majority of your 18 research? 19 MS. AHERN: Objection to form. 20 A. It depends on how you define 21 that. I mean, I think -- I think 22 characterizing the genomics of ovarian cancer 23 in relationship to utilizing that to better</p>	<p style="text-align: right;">Page 15</p> <p>1 from genetics for me with regard to this? 2 A. Not really. I think they're 3 synonymous. 4 Q. Okay. 5 A. I think one aspect of genetics 6 that laypeople may think about is what 7 component of the patient contributes to the 8 tumor; in other words, abnormalities within 9 their germline. We work on that too. 10 Q. Is it fair to say that most of 11 the research you've done pertains to women 12 who already have ovarian cancer? 13 A. I would say that's 14 accurate. 15 Q. So is your focus typically, 16 when treating a patient, more geared toward 17 removing, killing, curing the cancer as 18 opposed to determining what may have caused 19 her cancer? 20 A. Well, again, I think our 21 scientific interest is both. But if you're 22 trying to better treat the cancer, obviously, 23 the patient has to have the cancer.</p>
<p style="text-align: right;">Page 14</p> <p>1 treat the disease and to understand how it -- 2 understand its origins, would be a good way 3 to put it. 4 Q. Tell me: How do you define 5 "genomics"? 6 A. Characterization of the nucleic 7 acids that comprise the genome cells. 8 Q. Are you focused on 9 carcinogenesis or something that occurs after 10 the cancer actually is formed -- 11 MS. AHERN: Objection to form. 12 BY MR. DEARING: 13 Q. -- when you're talking about 14 those type of genomics? 15 A. I would say both. In other 16 words, as I mentioned before, I think you can 17 use genomics to better treat the patients, 18 both because you can prognosticate, stratify, 19 look for therapeutic targets. The genomics 20 will also give you an idea about how the 21 tumor started. So we do a lot of work on 22 early detection. 23 Q. Can you distinguish genomics</p>	<p style="text-align: right;">Page 16</p> <p>1 Q. Have you ever suggested to a 2 patient what her cause of ovarian cancer was? 3 A. Well, when patients have 4 germline mutations of BRCA1, BRCA2, that 5 obviously is going to come up in the 6 conversation. Beyond that, not -- and we can 7 get into why this is -- not a lengthy 8 conversation about definitive causes for 9 ovarian cancer. 10 Q. And that brings up a good 11 point. When we're discussing causes of 12 ovarian cancer or if your patient came to you 13 and said, Doctor, what caused my ovarian 14 cancer, what level of confidence or assurance 15 are you ascribing to the word "cause"? 16 In other words, is it a 100 17 percent conviction that there is no doubt 18 this caused this, or is it a 51 percent, this 19 most likely caused your cancer? 20 MS. AHERN: Objection to form. 21 A. Well, I think that it depends 22 on what we think in that particular case is 23 the origin of the cancer. I think the</p>

<p style="text-align: right;">Page 17</p> <p>1 general consensus is, for germline mutations 2 within the Fantoni DNA repair pathway, that 3 those are contributing to the tumor with a 4 great deal of certainty. 5 Q. Are you saying 80 percent or 6 more? 7 MS. AHERN: Objection to form. 8 A. I hate to put a number on it, 9 because it's a little bit difficult. But for 10 BRCA1 and 2, there is just no issue. There 11 are other genes within the Fantoni pathway 12 which we're very suspicious they contribute. 13 We probably don't have enough cases to 14 definitively tell a patient what the 15 percentage is. 16 But then there's a large number 17 of patients who come in who have ovarian 18 cancer for which they don't have germline 19 mutation. There, I don't think we can 20 definitively say what caused the tumor, but a 21 lot of us suspect that it's errors in DNA 22 repair that's occurring within the target 23 tissue.</p>	<p style="text-align: right;">Page 19</p> <p>1 published or co-authored a study that looked 2 at environmental factors or causative factors 3 other than germline mutations? 4 A. I certainly haven't led those 5 studies, and I don't think I'm actually on 6 any of the studies. I'm on a lot of what we 7 call SNP studies, where we're looking at 8 single nucleotide polymorphisms. These are 9 very large studies, looking at -- again, 10 we're looking at the genetics of the person. 11 I think that's different than what you're 12 asking me. 13 Q. It is. And I want to step out 14 of the world of genetics and look at the 15 other 70 percent of cancers and talk about 16 environmental contribut- -- 17 A. Again, I would just 18 emphasize -- I understand that. But some of 19 this may be definition, which is those 70 20 percent may very well be resulting from 21 genomic abnormalities, but it's just not 22 germline. 23 Q. Sure. And when you're talking</p>
<p style="text-align: right;">Page 18</p> <p>1 Q. Would you agree that fewer than 2 20 percent of ovarian cancers are caused by 3 some germline mutation? 4 MS. AHERN: Objection to form. 5 A. I think it's actually higher 6 than that. I think we're up around 30 7 percent. 8 Q. So that leaves, in your 9 opinion, 70 percent of ovarian cancers are -- 10 must have some other cause other than 11 germline mutations, correct? 12 MS. AHERN: Objection to form. 13 A. I think that's a -- I think the 14 data for that is pretty robust at this point. 15 Q. Have you ever researched 16 environmental factors that may contribute to 17 ovarian cancer when you're considering 18 causation? 19 A. We haven't done specific work 20 in our lab -- in my lab, focused on that. 21 Q. Have you ever participated in 22 any kind of study like that? You've 23 published quite a few studies. Have you ever</p>	<p style="text-align: right;">Page 20</p> <p>1 about -- let me rephrase the question, then. 2 Do you agree with me that fewer 3 than 30 percent of women with ovarian cancer 4 test positive for germline mutations or any 5 genomic abnormalities? 6 MS. AHERN: Objection to form. 7 A. Germline. 8 Q. Pardon me? 9 A. Germline. 10 Q. Just any genomic mutations or 11 abnormalities. 12 MS. AHERN: Same objection. 13 A. Well, if you look at all 14 ovarian cancers, they're all going to have 15 genomic abnormalities, the tumors. 16 Q. Maybe I need you to define that 17 for me. 18 A. So if you look at the 19 high-grade serous ovarian cancer, which is 20 what we're talking about, 100 percent of them 21 are going to have pB3 mutations. 22 Q. Okay. 23 A. The pB3 mutations almost</p>

<p style="text-align: right;">Page 21</p> <p>1 certainly contribute to the development of 2 the tumor. About 50 percent of them on top 3 of that is going to have an abnormality in 4 the Fantoni DNA repair pathway. That's going 5 to contribute to the development of those 6 tumors.</p> <p>7 I think the points that we're 8 discussing is how many of those come from a 9 germline mutation where you see an 10 abnormality in every cell of the body. 11 That's 30 percent. The other 70 percent are 12 having -- it's occurring within the target 13 tissue. I mean, as, unfortunately, 14 Dr. Vogelstein put it poorly, he said it was 15 bad luck. It's an abnormality in DNA repair. 16 You get a mutation in p53 that initiates the 17 process and then perhaps have a second hit or 18 a third hit, you get a tumor.</p> <p>19 Q. Do you have an opinion as to 20 whether the pB3 mutations are occurring 21 because of the original disruption in DNA or 22 are you suggesting that it's those mutations 23 that actually started the cancer?</p>	<p style="text-align: right;">Page 23</p> <p>1 don't consider yourself an expert in either 2 of those fields, correct? 3 A. Correct. 4 Q. And I don't mean that to be 5 critical. It's just everything is 6 specialized these days. 7 Do you have an opinion as to 8 what causes ovarian cancer? I'm sorry. Let 9 me break that down. That will take forever. 10 Do you agree that ovarian 11 cancer is multifactorial and that most 12 ovarian cancers have probably more than one 13 cause? 14 MS. AHERN: Objection to form. 15 BY MR. DEARING: 16 Q. With the exception of BRCA1 and 17 BRAC2 mutations, which may not? 18 MS. AHERN: Objection to form. 19 A. Well, I think -- I think it's 20 safe to say that ovarian cancer is a disease 21 of genomic chaos, and how you get to that 22 could be multifactorial. Patients could 23 inherit a gene, they could get an abnormality</p>
<p style="text-align: right;">Page 22</p> <p>1 MS. AHERN: Objection to form. 2 A. Both. So there's an 3 abnormality in DNA repair, the mutation 4 occurs spontaneously and pB3 isn't repaired. 5 And then, because pB3 affects DNA repair, the 6 DNA repair process becomes even worse, 7 setting off a cascade. 8 Q. Do you consider yourself an 9 expert in the field of epidemiology? 10 A. No. 11 Q. Do you consider yourself an 12 expert in the field of pathology? 13 A. No. 14 Q. Do you consider yourself an 15 expert in the field of analytical microscopy? 16 A. No. I will say parenthetically 17 I have epidemiology experience because of 18 medical school and pathology. You can't be a 19 practicing medical oncologist unless you know 20 some of that. 21 Q. Right. But there are people 22 with the working knowledge in your field, and 23 then there are experts in the field. And you</p>	<p style="text-align: right;">Page 24</p> <p>1 in a gene germline, they could be the 2 founder, or they could just have, again, a 3 spontaneous mutation within the target 4 tissue -- we call that sporadic ovarian 5 cancer -- producing this genomically unstable 6 cell type which then leads on to cancer 7 formation. I think the preponderance of the 8 evidence would suggest that that's the case. 9 Q. The preponderance of the 10 evidence suggests that most cancers are 11 multifactorial in origin? 12 MS. AHERN: Objection to form. 13 A. That ovarian cancer is a 14 disease of genomic chaos. 15 Q. Okay. Well -- 16 A. And I point that out because, 17 if you look at the molecular patterns through 18 different epithelial cancers, ovarian cancer 19 stands out. It's got very large shifts of 20 DNA that you don't see in other tumors. It 21 has very few mutations outside of BRCA1, 22 BRCA2 or p53. You don't see that in other -- 23 you don't see that in glioblastoma; you don't</p>

<p style="text-align: right;">Page 25</p> <p>1 see that in lung cancer; you don't see that</p> <p>2 in gastric cancer.</p> <p>3 So one of the ways to reconcile</p> <p>4 that is that this is a disease of a very</p> <p>5 severe DNA repair deficiency.</p> <p>6 Q. When you referred to -- I think</p> <p>7 you used the term "genomic chaos." Is that</p> <p>8 what you --</p> <p>9 A. Yeah.</p> <p>10 Q. When you talk about genomic</p> <p>11 chaos, are you referring to the state that</p> <p>12 exists after a cancer is formed, or are you</p> <p>13 saying that the cancer arises out of this</p> <p>14 chaos?</p> <p>15 A. Well, yeah, I think it's both.</p> <p>16 Most of the evidence we have suggests that</p> <p>17 the p53 mutation that I mentioned, occurring</p> <p>18 in 100 percent of high-grade serous ovarian</p> <p>19 cancers occurs very early, very early. So</p> <p>20 that would suggest that the genomic</p> <p>21 instability that p53 is contributing to is</p> <p>22 occurring very early in developmental cancer.</p> <p>23 Q. Right. But don't most studies</p>	<p style="text-align: right;">Page 27</p> <p>1 that you can duplicate in the lab?</p> <p>2 A. You can knock out the gene.</p> <p>3 You can use CRISPR to mutate it, yes.</p> <p>4 Q. Have you done those kind of</p> <p>5 experiments?</p> <p>6 A. I haven't done that. But in</p> <p>7 ovarian cancer models, there are now mouse</p> <p>8 models. Knocking out p53 was one of the</p> <p>9 genes that's been used. You can also knock</p> <p>10 out BRCA1 and BRCA2, and they produce animal</p> <p>11 models that look very close to human ovarian</p> <p>12 cancer.</p> <p>13 Q. Have you ever seen any p53</p> <p>14 models involving epithelial ovarian cells,</p> <p>15 human epithelial ovarian cells?</p> <p>16 MS. AHERN: Objection to the</p> <p>17 form. Are you saying animal models</p> <p>18 using human --</p> <p>19 MR. DEARING: No.</p> <p>20 MS. AHERN: Sorry.</p> <p>21 BY MR. DEARING:</p> <p>22 Q. Have you ever seen p53 models</p> <p>23 using human epithelial ovarian cells?</p>
<p style="text-align: right;">Page 26</p> <p>1 suggest that the p53 mutations are actually a</p> <p>2 product of the original carcinogenesis and</p> <p>3 disruption of DNA chain?</p> <p>4 MS. AHERN: Objection to the</p> <p>5 form.</p> <p>6 A. So the mutation has to occur.</p> <p>7 You know, again, our view on this is that</p> <p>8 it's probably occurring in most -- many of</p> <p>9 your cells on a regular basis. In this</p> <p>10 particular case, it's not repaired, and so</p> <p>11 then it leads to a different cascade. So is</p> <p>12 there some other abnormality for DNA repair</p> <p>13 in those target cells? It's certainly</p> <p>14 possible.</p> <p>15 Q. Does the p53 mutation interfere</p> <p>16 with the DNA repair process, or is it a</p> <p>17 product of the DNA's failure to repair?</p> <p>18 A. Both. Yeah.</p> <p>19 Q. Would you say that one is of</p> <p>20 greater prevalence than the other?</p> <p>21 MS. AHERN: Objection to form.</p> <p>22 A. I can't say that.</p> <p>23 Q. Are the p53 mutations something</p>	<p style="text-align: right;">Page 28</p> <p>1 A. Yeah. You're going to need to</p> <p>2 define that better. Are you saying taking</p> <p>3 human tumors and putting them into</p> <p>4 immunocompromised animals, PDX models?</p> <p>5 Q. No. I'm not talking about</p> <p>6 animal studies at all. I was talking about</p> <p>7 whether these p53 mutations were something</p> <p>8 that you can duplicate in the lab. And you</p> <p>9 said, well, there are some animal models that</p> <p>10 allow you to knock out the p53 and the BRCA1</p> <p>11 and BRAC2.</p> <p>12 My question is: Have you seen</p> <p>13 any p53 models of just human epithelial</p> <p>14 ovarian cells or seen experiments involving</p> <p>15 human epithelial ovarian cells where you can</p> <p>16 knock out p53 and BRCA1 and BRCA2? In other</p> <p>17 words, demonstrate that in a lab?</p> <p>18 MS. AHERN: Objection to form.</p> <p>19 A. When you say "human ovarian</p> <p>20 epithelial," are you talking normal --</p> <p>21 Q. Yes.</p> <p>22 A. -- human ovarian surface --</p> <p>23 Q. Normal or cancerous.</p>

<p style="text-align: right;">Page 29</p> <p>1 A. Well, so the cancer cells 2 already have it, so that experiment can't be 3 done. But human surface epithelium has been 4 taken and actually has been immortalized 5 using SV40 large T, which -- and small t, 6 which actually activates both RB and p53. So 7 that's a substitute, if you will. 8 Q. Right. 9 A. So there are those in vitro 10 models; not very good ones, I have to say. 11 But that's been attempted. You can also use 12 telomerase to immortalize. 13 Q. And there's nothing inherently 14 problematic in using immortalized cells, 15 right, for these experiments? 16 MS. AHERN: Object to the form. 17 A. Well, the challenge in the 18 ovary field is that -- and we have done some 19 of these experiments. We've used surface 20 epithelium as the normal control. There's a 21 lot of debate now about that, because the 22 feeling is some of it is coming from the 23 fallopian tube. So fallopian tube epithelium</p>	<p style="text-align: right;">Page 31</p> <p>1 manipulating these genes, most of which are 2 involved in DNA repair that are also found in 3 human tumors mutated, and you're getting 4 something that looks a lot like ovarian 5 cancer. 6 Q. The Baylor model is a mouse 7 model, correct? 8 A. Correct. That's right. 9 Q. But back to the original 10 question. You agree that there's nothing 11 inherently problematic in studying these 12 mutations using immortalized human epithelial 13 cells, right? 14 MS. AHERN: Objection to form. 15 A. I'm not quite sure what you're 16 asking. I mean, there's nothing -- there's 17 nothing wrong. It may not give you the 18 informed information that you want. 19 Q. Okay. How could an 20 immortalized cell give you inaccurate 21 information when you're looking at, for 22 example, neoplastic changes in cells exposed 23 to some agent?</p>
<p style="text-align: right;">Page 30</p> <p>1 may be more important. That's one sort of 2 controversial issue. 3 The second is that cell lines 4 are cell lines, so cell lines are convenient 5 models that we use, but they're far afield 6 from the human situation, so there are some 7 limits. 8 Q. Sure. I guess the best we can 9 use, right? 10 A. Well, there's now a lot of work 11 in animals, transgenic, you know, manipulated 12 adenovirus, Cre-Lox. Ronny Drapkin has, I 13 think, you know, a PAX8 driven -- I think 14 it's a p53 and BRCA knockout. They produce 15 ovarian cancers that look just like human. 16 There's a large T model from 17 Fox Chase which is less well-accepted because 18 it's a virus but nevertheless looks like 19 ovarian cancer. And then there's the Baylor 20 model, which used Dicer knockdown and BRCA 21 knockout, which also produces something that 22 looks a lot like ovarian cancer. 23 So the idea here is that you're</p>	<p style="text-align: right;">Page 32</p> <p>1 A. So, you know, in the history of 2 cancer biology and transformation, there's 3 always been a gap between cell line work and 4 what we call the measures of malignancy and 5 transformation and what one finds in animals 6 and then in humans. 7 So, for instance, you can put 8 some cell lines into -- some cancerous cell 9 lines into 3D cultures, you know, soft agar 10 cultures, and you get clusters. That's felt 11 to be a surrogate for malignancy, except for 12 when you take those cell lines and put them 13 into animals, which is felt to be a better 14 model, they don't make tumors. So there's a 15 disconnect. But we do a lot of work with 16 cell lines, because it's convenient. 17 Q. When you say "cell lines," 18 you're also including the immortalized cell 19 lines? 20 A. That's right. 21 Q. That was a tangent. Sorry. 22 So other than the BRCA1 and 23 BRCA2 mutations we discussed, do you have any</p>

<p style="text-align: right;">Page 33</p> <p>1 opinions as to whether there are any 2 established causes of ovarian cancer? 3 And I'm not just talking about 4 genomics in anything. 5 A. So, you know, again, it gets 6 into this area which is challenging in terms 7 of risk factors versus causality. 8 Q. And I'm going to talk more 9 about risk factors later. I want to use your 10 level of confidence in causation that we 11 discussed and ask you, other than these 12 germline mutations, is there any other factor 13 or -- not risk factor -- any other cause of 14 ovarian cancer that you're aware of? 15 MS. AHERN: Objection to form. 16 A. I think, in the spectrum of 17 what we're talking about with BRCA1 and BRCA2 18 and the Fantoni pathway, there's nothing that 19 comes close to that. 20 Q. Do you agree that asbestos can 21 cause ovarian cancer? 22 A. No. 23 Q. You disagree with IARC on that?</p>	<p style="text-align: right;">Page 35</p> <p>1 where patients were exposed to, really, 2 industrial doses of this material. And it 3 demonstrates a -- in a -- I think in some way 4 unconvincing fashion of an increased number 5 of ovarian cancers. These are small 6 studies -- very small studies. In fact, 7 there's even one meta-analysis that says if 8 one patient -- if one patient is 9 misclassified, you no longer have statistical 10 significance. 11 So I think it's interesting, 12 the epidemiologic data with ovarian cancer, 13 but not convincing. 14 And then the sleight of hand is 15 to say that that is relevant to what we all 16 are treating on a daily basis in terms of 17 ovarian cancer patients, because these 18 ovarian cancer patients aren't sitting in 19 asbestos factories. So I think if you put 20 all that together, it's not convincing to me 21 that asbestos causes ovarian cancer in what's 22 relevant here, which is we're asking for sort 23 of run-of-the-mill ovarian cancer.</p>
<p style="text-align: right;">Page 34</p> <p>1 A. I think they were premature in 2 making that conclusion. Yeah. 3 Q. Do you believe asbestos causes 4 mesothelioma? 5 A. Yes. 6 Q. Do you believe asbestos causes 7 other types of lung cancer? 8 A. Correct. 9 Q. But in your mind, it doesn't 10 cause ovarian cancer? 11 A. Correct. 12 Q. Is that because you don't 13 believe ovaries get exposed to asbestos or 14 because of some other reason? 15 A. Well, the data that supports 16 the IARC conclusion, to me, is in many ways 17 tangential. So they rely on the relationship 18 of mesothelioma and lung cancer with asbestos 19 to demonstrate the biology, carcinogenic, 20 enormously high risk those patients are for 21 those tumors. 22 They rely on that, and then 23 they look at a number of studies for ovary,</p>	<p style="text-align: right;">Page 36</p> <p>1 Q. Do you have any opinions as to 2 whether asbestos can cause any other type of 3 gynecologic cancers? 4 A. I know of no data for 5 endometrial/cervix. Those are the two really 6 big ones outside of ovary. As you know, 7 cervix cancer is an HPV-driven tumor. 8 Endometrial cancer is a little bit like 9 ovary, but probably driven by estrogen. 10 Q. What about ionizing radiation? 11 Do you think radiation might cause ovarian 12 cancer? 13 A. We went through that before. 14 You know, certainly ionized -- 15 MS. AHERN: Yeah, a lot of this 16 was already covered. 17 MR. DEARING: I'm sorry. I 18 promise, I'm not going to do this 19 all day. 20 MS. AHERN: So at some point 21 I'm going to probably cut you off 22 and see if we're going to go case 23 specific at some point.</p>

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1 MR. DEARING: I only read about
2 half of that deposition, because I
3 fell asleep. I'm sorry.
4 A. It's difficult to read.
5 Well, I can simply say, look,
6 ionized radiation is a documented mutagen,
7 and so it has a carcinogenic effect on
8 multiple epithelial layers.
9 It's hard to answer that
10 question, because we don't have a cohort of
11 patients necessarily that have had the kinds
12 of doses of radiation to the groin and the
13 ovaries.
14 Q. Not in this country.
15 A. Yeah. So I think -- I don't
16 know of convincing data that's true. I
17 wouldn't be shocked if you had patients who
18 had low-dose radiation to the surface of the
19 epithelium, that they might have some
20 pathologic changes.
21 Q. What about cigarette smoke? Do
22 you think cigarette smoke causes or
23 contributes to cause ovarian cancer?

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1 A. I have not seen any data
2 consistent with that. It does cause an
3 increased risk of cervical cancer.
4 Q. Well, your opinions about
5 causation we've just discussed, I assume they
6 also apply to high-grade papillary serous
7 ovarian cancers specifically?
8 A. Right.
9 Q. I read in your report you said
10 90 percent of epithelial ovarian cancers
11 arise from a single multi-dysfunctional cell.
12 Can you just put that in layman's terms, what
13 you meant by that? It might have been in
14 your deposition.
15 MS. AHERN: Do you have a copy
16 of the report? I don't remember
17 that specifically myself.
18 A. It's okay. I think --
19 Q. Do you agree with that
20 statement? Let me just ask it that way. Do
21 you agree that 90 percent or so of epithelial
22 ovarian cells arise from a single
23 multi-dysfunctional cell?

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1 MS. AHERN: Objection to form.
2 A. I think what that implies is
3 that we have no data to suggest that ovarian
4 cancer arises from a field defect. Right?
5 So if you look at, for instance, lungs that
6 have been exposed to cigarette smoke or
7 smokeless tobacco patients, for instance,
8 they'll have a field effect throughout the
9 entire mouth, multiple clones of cells that
10 are either premalignant or becoming
11 malignant.
12 If you look at the cervix with
13 HPV infection, you actually can find multiple
14 dysplastic lesions, because that's where the
15 virus is hitting. You don't see that in
16 ovarian cancer. We have no data to suggest
17 it's multiclonal initially.
18 Q. Well, there's certainly the
19 issue of synchronous tumors. Do you believe
20 that synchronous tumors just have their own
21 separate etiologies?
22 MS. AHERN: Objection to form.
23 A. So they're rare. They're not

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1 common. And if you believe David Huntsman's
2 data, what is thought to be synchronous, you
3 look at a molecular level, it's actually
4 metastasis. So I think that's a little bit
5 of a murky field. There may be true
6 synchronous tumors. I don't know if it's
7 just bad luck or is there another agent?
8 Don't know.
9 Q. Well, you would agree that
10 pathologists routinely make diagnoses of
11 synchronous tumors, right?
12 A. Yeah. And I think that's --
13 David -- I don't know if you know David up in
14 Vancouver. He's a pathologist. They pretty
15 much cast him out of the club, because he's a
16 spectacular molecular biologist, and he has
17 published a number of papers, particularly
18 ones that reported endometrial cancer along
19 with an ovarian cancer which was thought to
20 be two separate tumors and said no, the
21 molecular data is very clear; this is a
22 metastasis. The pathologists have actually
23 argued and said, no, they look different.

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1 Molecular biology doesn't lie.
2 Q. In those studies, have they
3 seen transitional cells where a serous may be
4 transitioned into endometrioid, or vice
5 versa?
6 MS. AHERN: Objection to form.
7 A. Well, I'm referring to
8 endometrial cancer and serous, not
9 endometrioid.
10 Q. Okay.
11 A. That's a separate question,
12 which is actually quite interesting. And I
13 do think there's some evidence that there can
14 be differentiation states, where the same
15 tumor can then differentiate. It's probably
16 an epigenetic change where it looks different
17 under the microscope, but it's the same
18 tumor.
19 Q. Would there be any way to tell
20 with any reasonable degree of medical
21 certainty that a serous tumor somehow morphed
22 into an endometrioid tumor or vice versa?
23 A. Well, I'll give you a good

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1 example of that. There's tumors called
2 carcinosarcomas. They are over the ovary and
3 the endometrium. If you take the sarcoma
4 part and you take the carcinoma part and you
5 do a molecular analysis on them for mutation,
6 they're identical; they're the same tumor.
7 But they look completely different under a
8 microscope because of methylation in
9 epigenetics. So there's your example.
10 Q. Well, I've seen cases where the
11 diagnosis of synchronous tumors was made by a
12 pathologist and they're two clearly distinct
13 histologies, serous and endometrioid.
14 Actually, I think I saw serous and clear
15 cell.
16 But regardless, is it your
17 opinion that we're actually most likely
18 talking about one tumor that metastasized,
19 regardless of the change in histologies?
20 MS. AHERN: Objection.
21 A. My view would be, more often
22 than not, that's what you're dealing with.
23 Q. Would there be any way to tell

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1 which one comes first, or would that just be
2 on a case-by-case basis?
3 A. That -- the timing -- temporal
4 relationship for that would be tough. It
5 would be a case-by-case basis.
6 MS. AHERN: I just want to move
7 things along to the case-specific
8 questions. She doesn't have
9 synchronous tumors, she doesn't
10 have endometrioid tumors.
11 BY MR. DEARING:
12 Q. You agree that Ms. Brower was
13 diagnosed with high-grade papillary serous
14 carcinoma?
15 A. Correct.
16 Q. Have you looked at the
17 pathology report in this case? I think I saw
18 it on your list.
19 A. I believe so, yes. It was
20 diagnosed as a high-grade papillary serous
21 tumor.
22 Q. Is there anything in that
23 pathology report or anything about the

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1 pathology opinions from her doctors that you
2 disagree with?
3 A. Do you have a copy of it?
4 Q. I do.
5 A. I have to say reflexively it
6 struck me as pretty routine.
7 Q. Sorry. This copy has my
8 highlighting on it.
9 A. That will help me.
10 Q. Nothing too scary.
11 MR. DEARING: Do we need to
12 mark that as an exhibit or just --
13 MS. AHERN: It's up to you.
14 MR. DEARING: I don't think we
15 need to.
16 MS. FOSTER: While he's
17 reviewing that, can we have an
18 agreement that an objection for one
19 is good for both?
20 MR. DEARING: Always.
21 A. So the final pathologic
22 diagnosis seems very straightforward to me.
23 Pap serous and it's, unfortunately, all over.

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1 Q. I just want to make sure when
2 we get to trial you don't say, oh, well, this
3 pathologist missed the boat on this
4 diagnosis, which has happened once.
5 MS. AHERN: Well, I guess
6 you'll have to wait to depose the
7 pathologist.
8 MR. DEARING: I can't wait.
9 I've deposed him four times. It's
10 always fun.
11 BY MR. DEARING:
12 Q. Do you have any opinions as to
13 whether talc played any role in Ms. Brower's
14 ovarian cancer?
15 A. I don't think it did.
16 Q. Do you agree that talc causes
17 an inflammatory reaction in peritoneal
18 tissue?
19 MS. AHERN: Objection to form.
20 A. So, again, we did -- we've
21 talked about this before. I think it depends
22 on how you define "inflammatory." I think
23 the general reflex for many people is

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1 inflammatory is sort of what you see with an
2 allergic reaction, it's what you see with the
3 infectious process.
4 The effects of talc, as you may
5 know, is granuloma formation. It's more of
6 a -- there certainly is a reaction, and it's
7 more of a foreign-body reaction, where the
8 body is trying to essentially get rid of this
9 thing that's not supposed to be there. So
10 that's been documented, both in the pleural
11 cavity and peritoneum.
12 Q. Would you consider macrophage
13 activity as a foreign-body response?
14 A. Yes.
15 Q. Have you reviewed the reports
16 or testimony of any of the plaintiffs'
17 experts in preparation for today or just in
18 the review of materials about this case?
19 A. Yes. I reviewed -- so I viewed
20 many of them for the previous one, and
21 then -- was it Plunkett?
22 Q. Right. Dr. Plunkett,
23 Dr. Godleski. Well, let's start with

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1 Dr. Godleski. Have you reviewed his report?
2 A. I don't think I reviewed it for
3 this case. Do you have it?
4 Q. I don't think I do. Let me
5 just tell you, he reported that he found, I
6 think, 21 talc fibers in the small amount of
7 tissue that he studied under SEM.
8 MS. AHERN: Objection to form.
9 I think you said talc "fibers," and
10 I don't think he actually recorded
11 fibers.
12 MR. DEARING: Okay. Let me
13 restate it.
14 BY MR. DEARING:
15 Q. As I recall, he found
16 approximately 21 talc particles in the
17 gynecologic tissue that he analyzed under
18 scanning electron microscopy. Do you have
19 any opinions about whether that's an accurate
20 finding?
21 A. Again, this issue always comes
22 up. So I've -- I have reviewed a lot of his
23 work of previous cases. Usually, when those

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1 entities are discovered or seen, there's no
2 inflammatory reaction seen at all in the
3 specimen. So, to me, that is problematic.
4 It raises the issue, if you look at what's
5 published in the literature, is how much of
6 this is actually reflecting what went on in
7 the patient versus what might be going on in
8 the lab with contamination and other issues.
9 So I don't know what that means.
10 Q. Okay. Well you're not
11 intending to challenge his finding of however
12 many talc particles --
13 A. He's finding something; I just
14 don't know if it's relevant.
15 Q. Well, he's finding talc, right?
16 Not "something." He's identified it by SEM
17 EDS as talc. Are you challenging that
18 finding at all?
19 A. No.
20 MS. AHERN: Objection to form.
21 BY MR. DEARING:
22 Q. When you said this issue always
23 comes up, you mean in these depositions or in

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1 the clinic or what? What do you mean by --
 2 A. Depositions. Yeah.
 3 Q. Do you agree that substances
 4 like talc can migrate from the perineum to
 5 the ovaries?
 6 A. Well, I don't think it's been
 7 definitively proven. You know, there have
 8 been a number of studies. There have been
 9 studies in animals, there have been some
 10 studies in human that there might be
 11 retrograde processes that deliver it. There
 12 are flaws with any of the studies. Some of
 13 them are using particles or materials that
 14 are different sizes than talc. Some of the
 15 other studies are in the setting of patients
 16 being examined, in terms of potentially
 17 delivering the material through the tubes.
 18 So I think -- I don't think we
 19 quite know definitively whether, in fact, and
 20 how much material could go from the vagina
 21 through the endometrium up into the ovary.
 22 Q. Well, if you've looked at
 23 Dr. Godles- --

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1 MS. AHERN: David, sorry; just
 2 to point out. This is covered ad
 3 nauseam. Migration translocation
 4 was covered by Russ for quite a
 5 while in the last deposition.
 6 MR. DEARING: I know, but I'm
 7 trying to be specific about
 8 Ms. Brower and then Dr. Godleski's
 9 findings --
 10 MS. AHERN: Okay. So this is
 11 leading up to -- I got you.
 12 MR. DEARING: Yeah. Yeah.
 13 MS. AHERN: Okay.
 14 BY MR. DEARING:
 15 Q. As you know from reading
 16 Dr. Godleski's report in this case, he didn't
 17 find just talc, he found quite a few other
 18 materials, hundreds of other materials, that
 19 he said were probably not talc, but they were
 20 also exogenous -- they weren't from within
 21 the body, they were from outside the body.
 22 So do you have an opinion about whether those
 23 findings are accurate or impossible?

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1 MS. AHERN: Objection to form.
 2 I think he said he hadn't read
 3 Dr. Godleski's report in this case.
 4 A. That's true.
 5 Q. Well, I'm telling you what's in
 6 the report.
 7 A. Okay.
 8 Q. He didn't just find talc. He
 9 found several other materials that he's
 10 calling exogenous, because the body doesn't
 11 make them, in the ovarian tissue and other
 12 gynecologic tissue, which, to me, supports
 13 the idea that other things besides talc could
 14 migrate from the perineum to the ovary.
 15 Do you have any opinions about
 16 that?
 17 A. Well, I don't think you can
 18 definitively say that didn't occur in the OR,
 19 didn't occur in the pathology suite, didn't
 20 occur as a contamination as he was doing his
 21 analysis. That's an alternative theory which
 22 I don't think his observations are going to
 23 disprove.

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1 Q. So to be clear, you believe
 2 that particles cannot migrate from the
 3 perineum to the ovary?
 4 MS. AHERN: Objection to form.
 5 A. No. What I said was that I
 6 don't think the evidence for that is
 7 conclusive.
 8 Q. What does that mean?
 9 A. It means you haven't produced
 10 the data to definitively say this occurs.
 11 Q. Would you agree that many
 12 scientists would disagree that the data is
 13 inadequate to substantiate transmigration of
 14 particles from the perineum to the ovary?
 15 MS. AHERN: Objection to form.
 16 A. Can you repeat that question?
 17 Q. Yes. Would you agree that many
 18 scientists have opined that materials like
 19 talc and other exogenous materials can
 20 migrate from the perineum to the ovary?
 21 MS. AHERN: Objection to form.
 22 A. I think some scientists have.
 23 But I don't think -- again, I don't think

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1 it's -- you know, I don't think the data is
2 conclusive that we know that, in a
3 quantitative way, that talc, other compounds
4 or other materials, can translocate
5 retrograde. How frequently does that happen?
6 The data, I think, is not overwhelmingly
7 compelling.
8 And we went through these
9 studies with Russ.
10 Q. I'm not going to go through
11 them all. I brought them, but I'm not going
12 to go through them.
13 I'm just trying to get a clear,
14 concise idea of your opinion on it with
15 regard to this case. So is it your opinion
16 that the talc that Dr. Godleski found in
17 Ms. Brower's ovaries did not come from
18 perineal use of talcum powder?
19 A. Yeah. As a scientist, I would
20 say he's observed something. It looks like
21 talc. He's also observed a lot of other
22 things. I'll buy that. I don't think, first
23 of all, he knows what all those other

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1 compounds are. And, two, I don't know -- I
2 don't think he knows or we know where it came
3 from.
4 Q. Are you saying it could not
5 have come from perineal talc use?
6 A. I would say we don't know where
7 it's coming from.
8 Q. That's a different answer. So
9 if you don't know, that at least leaves open
10 the possibility that it could be from
11 perineal talc use, right?
12 MS. AHERN: Objection to form.
13 Asked and answered.
14 MR. DEARING: I don't think it
15 was answered.
16 BY MR. DEARING:
17 Q. You can still answer it.
18 A. I think -- look, the issue is
19 do we know definitively where it came from?
20 We don't. And one of the problems with that
21 whole literature and everything that he's
22 done is he's not eliminated the possibility
23 of laboratory contamination. And that has a

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1 huge impact on this.
2 Q. Sure it does. And he goes to
3 great lengths to eliminate the possibility of
4 laboratory contamination.
5 Let me ask this question. And
6 it may be beyond your field, and that's fine.
7 You can just tell me.
8 So he uses a variable-pressure
9 SEM, which allows him to see below the
10 surface of the tissue to -- and into the
11 corpus of the tissue itself. And if he's
12 finding talc particles incorporated in the
13 tissue that are responded to by macrophages,
14 do you still think that's contamination?
15 MS. AHERN: Objection to form.
16 A. That is a little bit beyond my
17 area of expertise.
18 Q. Do you have any opinion as to
19 whether Ms. Brower's ovarian cancer actually
20 originated in the fallopian tube?
21 A. Well, they found a fallopian
22 tube tumor, I believe.
23 Q. They did.

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1 A. And the challenge that we
2 always have in these cases is chicken and
3 egg: Did it arise somewhere else and then
4 come down the tube, versus in the tube and
5 going out. So I don't definitively know.
6 There are components of her
7 case, though, in my opinion, strongly suggest
8 a genetic basis. That would then argue that
9 it may have come from the tube.
10 Q. Okay. I'm going to come back
11 to the genetics.
12 A. Okay.
13 Q. You haven't actually looked at
14 any of Ms. Brower's tissue itself, right?
15 A. No.
16 Q. So all of your review and
17 preparation for today and for your testimony
18 has been looking at reports of other people's
19 observations?
20 MS. AHERN: Objection to form.
21 A. Medical records and path, yeah.
22 Q. You wrote in your Swann report
23 that ovarian cancer is no longer considered a

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1 single disease but rather a composite number
2 of unique cancers characterized by completely
3 different patterns of genomic alterations and
4 different developmental origins.
5 Is it your opinion that
6 Ms. Brower's cancer is a composite number of
7 unique cancers --
8 A. No.
9 Q. -- as characterized by that
10 statement?
11 A. I'm sorry. What was that?
12 Q. As characterized by that
13 statement I just read?
14 MS. AHERN: Objection to form.
15 A. What that statement -- I can
16 elaborate a little bit on that statement. We
17 historically viewed ovarian cancer as ovarian
18 cancer. We now know that mucinous tumors,
19 clear cells, endometrioid, and high-grade
20 serous, which is what she had, are all
21 different diseases. She's got high-grade
22 serous. It's not a composite. It's
23 high-grade serous.

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1 Q. Sure. And that's the whole
2 reason for discerning the histology, right?
3 A. Correct. It's kind of
4 revolutionized the field, actually.
5 Q. That's not really new science.
6 It's been around a while, hasn't it?
7 A. Well, the --
8 Q. I mean, I know it's always
9 improving and changing.
10 A. The pathology has been around.
11 But we, as treating doctors, have ignored the
12 pathologists and treated everybody the same.
13 So now we are beginning to provide
14 personalized medicine for patients.
15 Again, she's got high-grade
16 serous, which is just high-grade serous.
17 Q. Having reviewed Ms. Brower's
18 medical records, do you agree that she
19 received the appropriate treatment from her
20 doctors for her cancer?
21 A. I think so, yes.
22 Q. Is there any type of treatment
23 that you would have done differently had she

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1 been your patient?
2 A. Not that I saw in the records.
3 She got, I think, really the standard of
4 care. And this is a bad disease.
5 Q. Does your opinion about ovarian
6 cancers deriving from the fallopian tube
7 depend in some aspect on histology? In other
8 words, are high-grade serous tumors more
9 likely to derive from the fallopian tube
10 than, say, an endometrioid carcinoma?
11 A. Correct.
12 Q. Okay. So serous would be the
13 most likely to derive from the fallopian
14 tube?
15 A. (Nodding head.)
16 MS. AHERN: Objection to form.
17 BY MR. DEARING:
18 Q. But in this case, you can't
19 tell whether the primary is the ovary or the
20 tube?
21 A. Clear cell and endometrioid are
22 thought to come from endometriosis. And
23 mucinous, we don't really know where they

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1 come from.
2 MR. DEARING: Do you guys need
3 to take a break?
4 (Recess from 9:43 a.m. to
5 9:51 a.m.)
6 BY MR. DEARING:
7 Q. Your opinions with regard to
8 Mrs. Brower's case, are they in any way based
9 on epidemiology studies?
10 A. Well, to look for risk factors
11 or how her tumor may have developed, you
12 know, we look at total ovulatory cycles, age
13 of menarche, age of menopause. Those
14 relationships have been developed by
15 epidemiologic studies to some extent.
16 Q. In your report in Swann, you
17 spent a good bit of ink talking about
18 epidemiology studies, you talked about the
19 cohort studies and the case control studies
20 and how you felt there was an inconsistency
21 between two of those. And I don't want to go
22 through all of that, but it was in your
23 report.

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1 But let me just ask you: Are
2 you basing any of your opinions about
3 Ms. Brower specifically on any cohort studies
4 or case control studies or information
5 contained in them?
6 MS. AHERN: Objection to form.
7 A. Well, the studies that I talked
8 about in the report were specifically the epi
9 studies and cohort studies related to talc.
10 Q. Right.
11 A. And my opinion really hasn't
12 changed about that in terms of how one
13 interprets it.
14 So in the context of that, when
15 I look at Mrs. Brower, I go, okay, this is a
16 patient I'm seeing; what's my general opinion
17 about where this tumor came from.
18 Q. Okay.
19 A. And so you will look about --
20 look to, I think, better documented risk
21 factors, again, like ovulatory cycles,
22 pregnancy, tubal ligation, and then, of
23 course, her family history.

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1 Q. Well, let's talk about that.
2 Specifically, in your opinion, what are the
3 risk factors that are generally accepted in
4 the gynecologic oncology community for
5 ovarian cancer --
6 A. Well, I think a --
7 Q. Let me be specific.
8 -- for papillary serous ovarian
9 cancer Ms. Brower has?
10 A. Well, we would look at age. So
11 she's 62, which is above the median age. So
12 that's going to be a risk factor for
13 developing ovarian cancer. It's a disease of
14 aging, to a certain extent. And then there
15 is a relationship between total ovulatory
16 cycles and risk of ovarian cancer.
17 Q. How does that apply to
18 Ms. Brower, total ovulatory cycles?
19 A. She had menarche at 12 and, I
20 think, menopause at -- somewhere in her 50s,
21 I think, which is a pretty big period of
22 time. So she would have excess ovulatory
23 cycles. Now, that's got to be

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1 counter-balanced by the fact that she had
2 three pregnancies.
3 Q. Right. That's what I was about
4 to ask.
5 A. And, of course, if you really
6 dig into the epidemiologic studies, which I
7 would not -- I would prefer not to. And I'm
8 not the expert on -- you can put these
9 formulas to say, okay, one pregnancy,
10 subtract a few points, blah, blah, blah.
11 The bottom line is three
12 pregnancies and tubal ligations would be
13 viewed as somewhat preventative for her,
14 potentially more than balanced by the early
15 menarche and late menopause.
16 Q. Is 12 years old early menarche?
17 MS. AHERN: Objection to form.
18 A. You know, I think across the
19 United States, particularly given her age,
20 back then, it would be. But you can go
21 into -- I mean, again, I'm not going to say
22 I'm an expert in that. But you can go into
23 urban populations and get slightly different

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1 age of menarche. To me, that is early and
2 that menopause is late.
3 Q. So is it your opinion that she
4 has a higher number of total ovulatory cycles
5 which places her at a greater risk from a
6 general population of women?
7 A. I would, yes.
8 Q. Okay. I thought she was kind
9 of right on the median line there.
10 A. Again, it could be
11 quantitative. How high is high? Is it just
12 slightly above? But again, the original
13 question was what are the factors you look
14 at.
15 Q. Right. So you've got age,
16 you've got total ovulatory cycles, which she
17 may or may not be on the high side of. Any
18 other established, you know, well-accepted
19 risk factors?
20 A. I think her family history is
21 impressive.
22 Q. Tell me about what stands out
23 about her family history?

<p style="text-align: right;">Page 65</p> <p>1 A. Well, her paternal grandmother 2 had ovarian cancer and breast cancer, so 3 breast/ovary syndrome is well documented. So 4 that's got to be noted. Then her father, 5 which is on the same side, obviously, I 6 believe, had colon and lung. Lung is 7 probably smoking related, but colon is in 8 there. So a fair amount of cancer. 9 And then on the maternal side, 10 both the mother and the grandmothers, I 11 recall, had bilateral mastectomies and 12 THBSOs. 13 So there are a couple of issues 14 here. First of all, if there was a 15 problem -- if there was a genetic basis on 16 the maternal side, because they had the 17 procedures, you might not see it. So you 18 have to recognize that. The flip side is, 19 why did they have those procedures? There 20 was some report about fibrocystic diseases in 21 the breasts. And my experience is that 22 having -- particularly given the age of these 23 patients, having bilateral mastectomies --</p>	<p style="text-align: right;">Page 67</p> <p>1 than we were 15 years ago to identify these 2 genes because we've learned more about it. 3 But to say categorically we know every 4 germline mutation in every gene that 5 predisposes a risk is not true. 6 And, in fact, if you look -- I 7 believe if you'll look at her genetic 8 counseling report, it basically says there 9 may be a genetic component of this that we've 10 missed. 11 Q. But just based on what you know 12 about genetic testing and your review of her 13 genetic testing profile and then results and 14 all of the mutations that were tested for, if 15 there was a relationship between her family 16 history of ovarian cancer/breast cancer and 17 her particular ovarian cancer, wouldn't you 18 expect it to have been revealed in all of 19 those mutations that were looked for? 20 MS. AHERN: Objection to form. 21 A. Well, the good news from my 22 perspective is she had state-of-the-art 23 genetic testing.</p>
<p style="text-align: right;">Page 66</p> <p>1 prophylactic bilateral mastectomies is just 2 very unusual. 3 Q. There was no evidence that 4 Ms. Brower had any fibrocystic breast 5 disease, right? 6 A. Not that I know of, no. 7 So, anyway, now you can say 8 look at genetic. She ended up having some 9 tests, and we discussed the tests. But I 10 think it's notable, very notable, about the 11 family history. It concerns me that there's 12 a genetic component here, as defined by the 13 family history, that may have been missed by 14 the testing. 15 Q. Well, if there was a genetic 16 component associated with the ovarian 17 cancer/breast cancer relationship, wouldn't 18 you have expected that to have shown up in 19 this panel of 30 gene mutations that were 20 tested? 21 MS. AHERN: Objection to form. 22 A. So I think the answer to that 23 is we are better -- we're in better stead now</p>	<p style="text-align: right;">Page 68</p> <p>1 Q. Right. 2 A. The bad news is, again, we just 3 don't -- we -- the state of the art is that 4 we don't know every single gene that causes 5 this disease. Genetic counselors have 6 admitted it and I, as a scientist, will say 7 that. 8 I mean, if you go back just 9 eight years ago, everyone thought it was 10 BRCA1, BRCA2. We didn't even know all of the 11 other germline mutations, ATM, ATR. So the 12 question is now, circa eight years further, 13 are there going to be a subset of other 14 genes -- rare, but a subset of other genes 15 that would explain this collection of 16 cancers? 17 Q. Right. 18 A. So it's -- because, again, it's 19 fairly impressive: Grandmother, ovary, 20 breast; father with colon; and now she's got 21 ovary. To me, that's -- from a -- from a 22 family history standpoint, I think there's 23 something going on there.</p>

<p style="text-align: right;">Page 69</p> <p>1 Q. Well, based on your vast 2 experience with genetics and your genomic 3 research, you would agree that the full panel 4 that she had makes up the vast majority, 5 overwhelming majority of mutations that 6 science currently knows about that might be 7 affiliated with a family history of breast 8 cancer or ovarian cancer? 9 MS. AHERN: Objection to form. 10 A. I would agree with that. 11 Q. And based on the current state 12 of the science, if there was a relationship 13 between her family history of cancers and her 14 ovarian cancers, it would have been revealed 15 in this genomic testing she had, right? 16 MS. AHERN: Objection to form. 17 BY MR. DEARING: 18 Q. Based on the science we know 19 today? 20 A. Well, I think the first 21 statement you said is true, which is that we 22 know there's a leftover group that have a 23 history like this that we think there's a</p>	<p style="text-align: right;">Page 71</p> <p>1 genetic counselors would be better for this, 2 because they see more of these patients. My 3 sense is that you're still missing, I would 4 say, 5 percent of ovarian cancer that has a 5 strong family history that's not showing up 6 there. 7 Q. Is that just based on your 8 experience or is that based on research, or 9 where did that 5 percent come from? 10 A. It's my experience. 11 Q. You don't believe that 12 Ms. Brower has Lynch Syndrome, do you? 13 A. Well, I think that the 14 components of Lynch, purely defined Lynch, is 15 on that panel. 16 Q. Right. And that was excluded, 17 correct? 18 A. Yes. 19 MS. AHERN: Objection to form. 20 A. Now, could she have a forme 21 fruste, you know, a newly -- it's a de novo, 22 new -- description of Lynch from another 23 gene?</p>
<p style="text-align: right;">Page 70</p> <p>1 genetic component that's not being identified 2 by that. That one, that's agreed. But I'm 3 not quite sure the second statement, which is 4 we already know this is not -- this is 5 negative, but she still has the family 6 history. So I'm raising the issue that, look 7 at our genetic testing. It's just not 8 complete at this point. 9 Q. Is there any way to quantify 10 the risk of her having some yet-undiscovered 11 genetic mutation that caused her ovarian 12 cancer? In other words, do you think it's, 13 like -- 14 A. We're really -- I mean, I see 15 what you're -- 16 Q. This makes up 100 percent of 17 what we know about, right? Is there any way 18 to quantify the percent of women who may have 19 a cancer like Ms. Brower has that's not 20 covered by this waterfront of genetic 21 testing? 22 MS. AHERN: Objection to form. 23 A. I think -- I mean, again, the</p>	<p style="text-align: right;">Page 72</p> <p>1 Q. Right. 2 A. Well, I don't know. 3 Q. Right. And here's -- 4 A. But not the classic Lynch 5 you're talking about. 6 Q. And here's the thing about this 7 case and trials in general, is that findings 8 are based on evidence. And so what I want to 9 ask is, there's no evidence of any gene 10 mutation or genetic syndrome that Ms. Brower 11 may have, correct? 12 MS. AHERN: Objection to form. 13 A. Well, there's evidence that she 14 may have a genetic component based on the 15 family history. 16 Q. Okay. But with regard to all 17 of the testing that was done, there was no 18 evidence revealed by any of her genetic 19 testing to suggest she has a genetic 20 predisposition to cancer, correct? 21 MS. AHERN: Objection to form. 22 A. Correct. 23 Q. Do you have any knowledge about</p>

<p style="text-align: right;">Page 73</p> <p>1 or understanding of the number of talcum 2 powder applications Ms. Brower may have had 3 during her lifetime? 4 A. What I saw in the record, if I 5 recall correctly, was starting roughly at age 6 17, I think, and then moving through -- not 7 quite -- there was some confusion. It wasn't 8 quite clear to me when she stopped using 9 actually the J&J product and then switched to 10 a different product. That was a little bit 11 vague to me. But there was certainly a 12 substantial period of time where she 13 continued to use a talc product that wasn't 14 J&J. 15 I don't know if that answered 16 your question. 17 Q. Well, let me just talk about -- 18 A. So total -- again, this is one 19 of the problems with even the epi studies, 20 which is how do you quantify this stuff? 21 Q. Well, have you looked at, at 22 least, what her -- at least yearly use, or 23 did you break down her use of talcum powder</p>	<p style="text-align: right;">Page 75</p> <p>1 evidence that suggests that talc causes 2 ovarian cancer. 3 Q. Do you believe there's some 4 evidence? 5 A. No. 6 Q. You believe there's no evidence 7 that talc causes ovarian cancer? 8 A. No convincing evidence. 9 Q. Do you know Dr. James Thigpen? 10 A. I do know Tate. 11 Q. Have you published with him? 12 Let me ask you: How do you know him? 13 A. So Tate was the vice chair of 14 the Gynecologic Oncology Group for years. 15 And I joined the group in 1991, and then sort 16 of worked my way through a number of 17 leadership positions. The Gynecologic 18 Oncology Group merged with NSABP and RTOG to 19 form NRG Oncology. And I remained one of the 20 chairs. So I've known Tate for probably 25 21 years. 22 Q. Have you ever actually worked 23 together?</p>
<p style="text-align: right;">Page 74</p> <p>1 by estimated number of applications or 2 anything like that, or was that relevant to 3 your opinions? 4 A. Well, I looked at it sort of in 5 a semi-quantitative way. I certainly didn't 6 calculate, you know, monthly applications and 7 issues on that. 8 Q. Well, if you don't believe that 9 talc can migrate from the perineum to the 10 ovary and you don't believe that talc causes 11 ovarian cancer, is there any reason for you 12 to even consider the number of talcum powder 13 applications she had? 14 MS. AHERN: Objection to form. 15 A. Well, this is -- so the purpose 16 of the case is obviously the role of talc in 17 the development of ovarian cancer. So as the 18 expert involved here, it was certainly my 19 obligation to make sure she had used it. 20 Q. Okay. But your opinion would 21 be the same whether she used it or not, 22 right? 23 A. I don't believe there's strong</p>	<p style="text-align: right;">Page 76</p> <p>1 A. Well, again, as a chair, and 2 he's the vice chair, I would consider that 3 working together in terms of developing 4 protocols in the clinical treatment of 5 ovarian cancer. He's also invited me to 6 Jackson twice to give a talk. 7 Q. Have you published with him -- 8 I'm sorry. Have you done any -- have you 9 conducted any clinical research with him? 10 A. I'm trying to think if we've -- 11 again, if you want to call clinical research 12 the administration of the Gynecologic 13 Oncology Group, then I'm heavily involved in 14 that, and he was too. If the definition of 15 clinical research means we were both on the 16 same protocol, I don't think actually we were 17 on any protocols together. We may have 18 ultimately published together on a couple of 19 papers. 20 Q. Okay. And I should have asked 21 you this early on. Do you have any ongoing 22 clinical trials or studies involving talc and 23 ovarian cancer?</p>

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1 A. Involving talc, no.
2 Q. Or involving any suspected
3 causative agent in ovarian cancer other than
4 genomics?
5 A. Nothing outside of genomics.
6 Q. I'm sorry. I drifted away from
7 our risk-factor discussions. Let me get
8 back.
9 So you talked about age, you
10 talked about total ovulatory cycles, and you
11 finished with family history. So you
12 mentioned the maternal grandmother with a
13 history of ovarian cancer and breast cancer
14 and Ms. Brower's father having colon cancer
15 and lung cancer.
16 A. Skin cancer, too, I believe.
17 I'm not sure if that's relevant.
18 Q. Do you know whether her father
19 was a smoker?
20 A. I thought it was mentioned
21 somewhere in the document.
22 Q. If her father was a longtime
23 smoker, would you attribute the lung cancer

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1 to that, most likely?
2 A. Probably, yeah.
3 Q. What about colon cancer? Can
4 colon cancer be associated with cigarette
5 smoking?
6 A. Not to my knowledge. If it is,
7 it's not a strong indication.
8 Q. Are you aware of any specific
9 links between Ms. Brower's father's colon
10 cancer and her ovarian cancer?
11 A. Well, we --
12 Q. Other than Lynch Syndrome
13 that we've already --
14 A. We touched on that. Lynch
15 would be about a three- to fourfold increase
16 risk for ovarian cancer.
17 Q. There's no evidence she has
18 Lynch Syndrome?
19 A. The classic definition,
20 correct.
21 Q. So is there any nexus, in your
22 mind, between her father's colon cancer and
23 her ovarian cancer?

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1 A. Beyond that, not that I know
2 of.
3 Q. And with regard to her
4 mother's ovarian -- I mean, her grandmother's
5 ovarian cancer and breast cancer -- first of
6 all, you only have opinions about her
7 paternal grandmother's cancer because it was
8 reported somewhere in the medical records,
9 right?
10 A. Yeah. Genetic counseling
11 document was pretty complete in terms of the
12 history of her family.
13 Q. Do you know what histological
14 subtype of ovarian cancer her grandmother
15 had?
16 A. No. I don't think that was
17 reported.
18 Q. Okay. Same thing with breast
19 cancer. Do you know what type of breast
20 cancer she had?
21 A. No.
22 MS. AHERN: You wouldn't happen
23 to have a copy of the genetic

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1 counseling record, would you?
2 MR. DEARING: I just have this
3 report. I don't have the full
4 record. I can't represent that
5 this is a complete copy of the
6 report. It's just something I put
7 in my notes. I'm not going to
8 spend any more time on it. But
9 you're welcome to look at my copy.
10 MS. AHERN: Thank you. This
11 might be the tumor.
12 A. Six maternal grands diagnosed
13 with breast cancer. I forgot that.
14 Yeah. So the father is
15 reported as a smoker here. Yeah. The rest
16 of it is pretty much discussed.
17 Q. Do you have any opinions about
18 whether relatives removed as far as great
19 aunts really have any influence over a
20 person's disposition toward ovarian cancer?
21 A. It's less -- it's certainly
22 less influential than, you know, first-degree
23 relatives.

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1 Q. And there are quite a few
2 studies about that. And they often will
3 exclude relatives beyond first degree as
4 relevant family history. Do you agree with
5 that?

6 MS. AHERN: Objection to form.

7 A. Yeah.

8 Q. Any other family history that
9 you're aware of that you feel may at all be
10 related to Ms. Brower's case?

11 A. That's about it.

12 Q. What about any other risk
13 factors? Are you aware of any other
14 established risk factors that may have
15 contributed to Ms. Brower's cancer?

16 A. I think that was the major list
17 that I reviewed. Yeah.

18 Q. Would you agree that genetic
19 predisposition is probably the most
20 compelling risk factor for ovarian cancer?

21 A. And how do you define
22 "compelling"?

23 Q. Well, the one risk factor that

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1 may have the most influence over a person's
2 predisposition to ovarian cancer?

3 MS. AHERN: Objection to form.

4 A. I think it has the biggest
5 impact. Yeah. So BRCA1, 80 percent lifetime
6 risk; BRCA2, maybe 40 percent. These are
7 highly penetrant genes.

8 Q. Right.

9 A. And then the other ones.

10 Q. I may have just asked you this,
11 but is it your opinion that there are no
12 other risk factors, in your opinion,
13 influencing Ms. Brower's ovarian cancer?

14 MS. AHERN: Objection to form.

15 A. None that I saw, you know, in
16 reviewing the records. That's really the --
17 I think that's an inclusive list.

18 Q. Did you consider any protective
19 factors in Ms. Brower's case that may apply
20 to her? We talked about the multiparity.
21 She had three children that may have
22 interrupted her ovulatory cycle for years.
23 Any other protective factors?

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1 A. We mentioned -- I may not have
2 made it clear, she's had a tubal ligation.
3 And that certainly is viewed, based on data,
4 to be protective.

5 Q. Any other protective factors
6 that you observed in her medical records or
7 family history or anything?

8 A. Not that I saw.

9 Q. I think --

10 A. I do think -- sorry. Because
11 it was unclear and short. She did have a
12 history of OCPs, birth control. But it
13 seemed to me maybe less than two years and
14 inconsistently used.

15 Q. Okay. And you list that as a
16 protective factor because it reduces her
17 number of ovulatory cycles?

18 A. Correct.

19 Q. Do you have any opinion as to
20 what caused Ms. Brower's ovarian cancer?

21 A. Well, again, I think -- I'm
22 impressed by the family history, and I really
23 wonder whether there's a undiagnosed germline

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1 abnormality. This would be a patient which
2 now we probably would do whole exome
3 sequencing. Back then, not standard of care
4 and expensive, so that would be a concern.

5 Now, if that was still
6 negative, again, as we discussed before, you
7 know, I think the consensus in the field is
8 that many of these tumors arise because of a
9 DNA repair abnormality that's arising right
10 in the cell called sporadic -- there's a
11 variety of names you could label that kind of
12 tumor. It's still a genomic basis.

13 Q. Right. So would you agree,
14 then, that for there to be a disruption in
15 the DNA repair process, there must be
16 something causing that disruption? In other
17 words, it doesn't just spontaneously stop
18 repairing itself for no reason, right?

19 A. Well, the abnormality and DNA
20 repair could also be spontaneous. As Hubert
21 Vogelstein says, bad luck.

22 Q. So is it your opinion that
23 there must be some genetic abnormality

<p style="text-align: right;">Page 85</p> <p>1 contributing to Ms. Brower's ovarian cancer 2 because that's essentially the only way these 3 cancers occur? 4 A. I think that -- my sense is the 5 consensus in the field -- and I'm part of 6 that -- is that, yeah, ovarian cancer arises 7 because of genomic abnormalities, and that's 8 coming from a DNA repair defect. Some of 9 that is coming from mom and dad or germline 10 event. A larger portion of it is occurring 11 spontaneously. 12 Q. And is it your opinion that 13 it's just not possible that a foreign body 14 may have reached the ovary, caused an 15 inflammatory reaction, a reactive oxygen 16 species reaction that may have disrupted the 17 DNA in that process? 18 A. There's not convincing evidence 19 for that. 20 Q. Are you saying that it's not 21 possible, or you're just not convinced that's 22 what happened in this case? 23 A. Well, I think in this</p>	<p style="text-align: right;">Page 87</p> <p>1 innuendos from a scientific standpoint. We 2 went through it before, we can go through it 3 again. There's just not any evidence, 4 convincing evidence, that that's -- that 5 that's occurring. 6 Q. One of the things you said in 7 your report was that you didn't feel there 8 was adequate experimentation with regard to 9 biologic mechanisms. To use your words, you 10 said that there was a lack of rigorous 11 biologic mechanistic experiments. Do you 12 remember that phrase? 13 A. Yeah. 14 Q. And you just told me that you 15 didn't think that's what happened in 16 Ms. Brower's case, that scenario I just 17 described with the foreign body reaction, et 18 cetera. What sort of rigorous biologic 19 mechanistic experiment would you need to see 20 before you were convinced that talc exposure 21 might have increased Ms. Brower's ovarian 22 cancer risk? 23 MS. AHERN: Objection to form.</p>
<p style="text-align: right;">Page 86</p> <p>1 particular case, I don't think it happened. 2 And I think that the more likely etiology of 3 her tumor is genetic, either spontaneously or 4 germally. 5 Q. Do you think that that 6 inflammatory process I just described is 7 possible? 8 MS. AHERN: Objection to form. 9 A. Just describe it again. 10 Q. Well, for there to be a foreign 11 body that ends up in the ovarian epithelial 12 cells which causes an inflammatory response, 13 which causes a reactive oxygen species or 14 reactive nitrogen species-type response, 15 which results in DNA damage, which 16 replicates, do you think that that is a 17 plausible or possible event in a woman's 18 life? 19 A. I don't think so. You know, 20 again, from a scientific standpoint, I have 21 to look at the available evidence. And we 22 can go through -- what you just described is 23 fairly complex, with lots of sort of</p>	<p style="text-align: right;">Page 88</p> <p>1 This was gone over ad nauseam with 2 Russ in terms of experimental or 3 experiments that could be done. 4 MR. DEARING: Can you give me 5 two minutes of it or three minutes? 6 I won't spend much time. 7 MS. AHERN: Okay. 8 MR. DEARING: I have three 9 questions. 10 A. We did go over it extensively, 11 because it's a good question. 12 I think if you look critically 13 at the biologic experiments, a lot of it 14 rests on the experiment that used 15 immortalized surface epithelium and then a 16 granulosa cell -- cell line -- which that 17 paper is just terrible. And I think I listed 18 it in the report. I went over it fairly 19 carefully, which is that the granulosa is 20 cell element has got nothing to do with 21 high-grade serous ovarian cancer. And then 22 the immortalized cells, we've talked about. 23 They're a model that people use. They're not</p>

<p style="text-align: right;">Page 89</p> <p>1 normal. All right? They have SV40 in them. 2 And then the readout in that 3 paper to show malignant transformation, which 4 is, from my perspective, completely 5 misleading, is soft agarose growth of those 6 cell lines. 7 Q. Now you're referring to the 8 Buz'Zard study, pycnogenols? 9 A. Yeah. Correct. I mean, the 10 problem there is that we've got those cell 11 lines. They grow in soft agar without doing 12 anything to them. So they're not normal. 13 That's not a measurable transformation. 14 There's nothing in that paper that convinces 15 me. 16 Now, there are other surrogate 17 papers where they look at gene expression 18 patterns, they looked at Rous generation. 19 That's all very tangential. Even the 20 quantitative measures of what they're looking 21 at are very subtle. So I look -- as a 22 scientist, step back and say, you know, what 23 does this mean in toto and compare it to what</p>	<p style="text-align: right;">Page 91</p> <p>1 A. Oxidative stress can have an 2 impact on DNA, yeah. 3 Q. What if the epithelial cells 4 exposed to talc cause a significant increase 5 in CA125 expression? Would that affect your 6 opinion at all on whether talc exposure can 7 cause ovarian cancer? 8 MS. AHERN: Objection to form. 9 A. Definitely not. 10 Q. Have you read the deposition 11 transcripts of Ms. Brower's treating 12 physicians? 13 A. Benedict Benigno. I think I 14 reviewed him, yeah. 15 Q. Dr. Tenney? 16 A. Meaghan Tenney. 17 Q. There weren't a lot of opinions 18 expressed in those depositions. But of what 19 you read, did you see anything that you 20 particularly disagree with in those 21 deposition transcripts? 22 MS. AHERN: And that you recall 23 today.</p>
<p style="text-align: right;">Page 90</p> <p>1 has been done in lung cancer and gastric 2 cancer, even glioblastoma. It just pales in 3 comparison in terms of convincing me of 4 providing data for the model you describe. 5 Right? 6 Q. If it could be demonstrated 7 that epithelial ovarian cells exposed to talc 8 significantly -- experience significantly 9 enhanced oxidative stress in those cells, 10 would that affect your opinion regarding talc 11 exposure and ovarian cancer? 12 A. Not substantively. It would be 13 an interesting observation. But oxidative 14 stress is a very broad category. There are 15 lots of things that cause oxidative stress 16 which kills cells, doesn't transform them. 17 Oxidative stress is involved in 18 cardiovascular disease, but that's not 19 cancer. 20 Q. Would you agree, oxidative 21 stress can certainly disrupt DNA repair, 22 right? 23 MS. AHERN: Objection to form.</p>	<p style="text-align: right;">Page 92</p> <p>1 A. As far as I recall, from a 2 clinical management standpoint, it was very 3 straightforward. 4 Q. Can you name the pharmaceutical 5 or cosmetic companies that you've received 6 research funding from? 7 A. Pharmaceutical and what? 8 Q. Cosmetic companies, like 9 Johnson & Johnson? 10 A. So I haven't received any 11 research funding from cosmetic companies. 12 Pharmaceutical, I think it's listed on my CV. 13 You'll see a lot of pharma because of the 14 clinical trials I run. So I'm not sure I can 15 give you an absolute list. But, you know, 16 it's the usual players: AstraZeneca, Pfizer, 17 Imogen; and these are all treatment trials 18 for new agents for ovarian cancer. And those 19 funds do not flow to me. They flow to the 20 hospital. 21 Q. With regard to the genomic 22 research that you've done, how was that 23 funded?</p>

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1 A. That's all NIH grants.
2 Q. Other than in this talcum
3 powder litigation, have you ever testified on
4 behalf of a pharmaceutical company before?
5 A. No. The Maine was a
6 malpractice case. This is the only example,
7 yeah.
8 Q. Do you presently sit on any
9 editorial boards or peer-review panels for
10 medical journals?
11 A. I'm an associate editor for the
12 Journal of National Cancer Institute, and I
13 do a lot of reviews. But that's about the
14 only editorial position.
15 Q. I'm sorry. You said associate
16 editor?
17 A. Associate editor, yeah. JNCI.
18 Q. Would your past editorial board
19 experience and peer-review committee
20 experience be identified in your CV?
21 A. Yeah. It will all be on there.
22 I mean -- yeah. I was on GYN/ONC and a
23 couple of other journals, but I'm off now.

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1 Q. And you've never published on
2 talc and ovarian cancer before, correct?
3 A. No.
4 Q. And have you ever lectured or
5 presented on the topic of ovarian cancer and
6 talcum powder?
7 A. No.
8 MR. DEARING: If we can just go
9 off the record for a few minutes, I
10 want to synthesize my notes.
11 (Off-the-record discussion from
12 10:29 a.m. to 10:36 a.m.)
13 BY MR. DEARING:
14 Q. I think I asked you if you ever
15 published or lectured on the relationship
16 between talc and ovarian cancer. Have you
17 ever conducted any cell studies involving
18 talcum powder?
19 A. No.
20 Q. Have you ever conducted any
21 ovarian cell line studies involving any kind
22 of reactive agent?
23 MS. AHERN: Objection to form.

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1 BY MR. DEARING:
2 Q. Other than talcum powder?
3 MS. AHERN: Objection to form.
4 Sorry.
5 A. It's a little -- it's a little
6 broad. But most of our work is genomic, and
7 we put in genes and we take out genes.
8 Q. Have you ever done any studies
9 where you intentionally exposed epithelial
10 cells to some agent and then studied the
11 reaction to it?
12 MS. AHERN: Objection to form.
13 A. Ovarian epithelial cells?
14 Q. Right.
15 A. We have attempted to
16 immortalize them. That would be viruses, but
17 that's a delivery system. It's a little
18 different, I think, than what you're asking.
19 Q. In the Buz'Zard study, did they
20 immortalize those cells with viruses?
21 A. So I don't think -- I think the
22 cell line in that paper, they didn't
23 immortalize. They got it from --

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1 Q. They bought it?
2 A. My guess is they got it from
3 Nellie Osberg, because she had the original
4 SV40 immortalized cell lines.
5 Q. I just couldn't remember. I
6 didn't remember these being virus.
7 I asked you about talc and its
8 ability to translocate from the perineum to
9 the ovaries, and you said there was no
10 convincing evidence to support that. Is your
11 opinion also true with regard to other things
12 like heavy metals?
13 Is your opinion the same with
14 regard to heavy metals a person may be
15 exposed to perineally?
16 MS. AHERN: Objection to form.
17 A. Retrograde, coming -- or
18 just --
19 Q. Right. Is there any way for
20 any materials -- let me just put it out there
21 in a very broad sense.
22 In your opinion, is there any
23 way that any material -- whether it be talc,

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1 heavy metals, asbestos, whatever -- can
2 migrate from the perineum to the ovaries
3 through the reproductive tract?
4 MS. AHERN: Objection to form.
5 A. Well, you know, we discussed
6 this before. There's an anatomical conduit.
7 Right? So it's not like it's blocked. So
8 theoretically, could something happen? Sure.
9 What I'm saying is I'm not convinced by the
10 talc data or the experiments that we reviewed
11 last time that we know that this happens
12 reproducibly and efficiently. Those
13 experiments are just not very well conducted.
14 And then I think the
15 observation, finding particles in tumors is
16 not convincing to me that that's coming from
17 that process. It's just an observation.
18 Q. And to be clear --
19 A. That's what I'm saying.
20 Q. -- Dr. Godleski's findings are
21 not just from tumor tissue. It's from other
22 tissue besides tumor tissue. Does that
23 affect your opinion at all?

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1 A. Well, it's tissue. I make it
2 broad.
3 Q. Are you aware of any other way
4 that talcum powder may have reached
5 Ms. Brower's ovaries? In other words,
6 through some other mechanism of transport,
7 either inhalation or whatever?
8 MS. AHERN: Objection to form.
9 A. Again, I don't -- I remain
10 unconvinced that that plays a role in her
11 ovarian cancer. There is data people talk
12 about or the possibility that high levels of
13 talc in the air can be inhaled and then get
14 into the lungs. I struggle with the -- I
15 struggle with that concept.
16 Q. Would you agree that it's
17 unlikely that inhaled talc particles or
18 inhaled asbestos particles, or whatever,
19 would have reached the ovaries in
20 Ms. Brower's case?
21 A. Unlikely. Yeah.
22 Q. I think I said very -- I meant
23 to say very unlikely. Would you agree with

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1 that?
2 A. Exceedingly unlikely, yeah. I
3 think if -- again, we -- if that's the
4 proposed mechanism, you would think you would
5 see something in the lung for all that talc.
6 Q. Although her lung tissue wasn't
7 studied in this case, so we don't know.
8 MS. AHERN: Objection.
9 A. She had a lot of scans.
10 Q. True. As I mentioned,
11 Dr. Godleski found actually 27 talc particles
12 in the gynecologic tissue. Do you have any
13 explanation for how they got there if you're
14 saying they can't migrate and it's not likely
15 she inhaled it?
16 Let me break that down. First
17 of all, do you take exception to the fact
18 that he found talc in the tissue?
19 MS. AHERN: Objection.
20 A. What do you mean by
21 "exception"? I think he's seeing something,
22 and we'll rely on him to say he can identify
23 that by mass spec that it's talc. But I

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1 don't know where it's coming from. It could
2 be the OR suite, it could be the pathology
3 suite, it could be his own laboratory.
4 Q. So your opinion is that has to
5 be contamination; there's no other way?
6 A. I think it's conceivable it's
7 contamination. And then I add that to all
8 the other experiments that were done where
9 you can see material in controls versus
10 tumors. There's a pretty strong suggestion
11 that contamination is a problem in these
12 experiments. So I don't -- you know, I don't
13 know where that's coming from as part of
14 the -- part of the problem with interpreting
15 his results.
16 Q. Well, you said it's conceivable
17 that it's contamination. If you were to
18 exclude contamination as the source of that
19 talc, do you have any other explanation for
20 how talc could have gotten there?
21 MS. AHERN: Objection to form.
22 A. That would be the major issue.
23 You know, then, theoretically, it might have

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1 come from the patient. It's odd that there's
2 no -- the additional complexity is if one
3 goes down that line, then what's the actual
4 role of it in that tumor. There's no --
5 really no inflammatory response. So that's
6 also confusing.

7 Q. Well, you're basing your
8 opinion that there's no inflammatory response
9 in this case by looking at the pathology
10 report, right? I mean, you haven't looked at
11 the tissue itself to see if there's an
12 inflammatory response, have you?

13 A. I would argue that even if I
14 looked at the tissue, I wouldn't be the
15 person to describe that. But I would assume
16 that it would be replete in the analysis from
17 the people who have looked, including, you
18 know, the individual who found the talc
19 particles. He would describe multiple
20 eosinophils and neutrophils and other
21 elements in inflammation.

22 Q. But you wouldn't expect the
23 surgical pathologist to have recognized

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1 foreign body reactions like macrophages or
2 granulomatous responses?

3 MS. AHERN: Objection to form.

4 A. Well, they would definitely
5 describe granulomatous responses.

6 Q. Okay. Well, you wouldn't
7 expect him to describe macrophage responses,
8 would you?

9 A. It depends on how severe it is,
10 yeah.

11 Q. I've looked at a hundred of
12 these. I don't think I've ever seen a
13 surgical pathologist recognize the presence
14 of macrophage activity, even though it's
15 there, because Dr. Godleski may have
16 subsequently found it.

17 So, I mean, my question is:
18 Would it be the normal practice for a
19 surgical pathologist to see and recognize
20 macrophage activity responding to foreign
21 bodies, foreign particles?

22 MS. AHERN: Objection to form.

23 A. Well, I think it was

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1 substantive. Yeah. I mean, the other
2 interpretation is it's really not there.
3 There's no granulomatous response at all.
4 There's no inflammatory response. And
5 Godleski is just looking at it, you know, and
6 he's seeing things.

7 Q. Well, would you agree that --

8 A. And the question is, too, if
9 you want to get down into the weeds on this,
10 is what kind of macrophage is he looking at?
11 Is this an M1 or an M2 macrophage?

12 Q. Would you agree that if he sees
13 macrophage activity associated with a foreign
14 particle, that he's attributed to be talc,
15 that that talc had to be there in the tissue
16 in vivo; in other words, before the tissue
17 was removed from the body?

18 MS. AHERN: Objection to form.

19 A. I actually wouldn't agree with
20 that.

21 Q. So macrophage activity can
22 continue even after the tissue is removed
23 from the --

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1 A. So macrophages are frequently
2 found in tumors.

3 Q. Right.

4 A. So those macrophages could be
5 there because there's a tumor there. And
6 then it's in the path suite, it's in his
7 laboratory, he gets some contamination of
8 talc. He puts them together as if that's
9 evidence that the talc was there and the
10 macrophages responded to it. But in fact,
11 none of the macrophages are there because the
12 tumor is producing cytokines and chemokines.

13 In fact, that's a very
14 well-documented process of ovarian cancer.

15 Q. My question is, really, does
16 the macrophage activity stop when the tissue
17 is removed from the body?

18 A. Say that again.

19 Q. Okay.

20 A. The macrophages are in the
21 tumor. When you remove the tumor, they go
22 with it.

23 Q. When the macrophages are in the

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1 tumor in the body, they're active, they're
 2 doing something, right? They're attempting
 3 to sequester foreign particles or invading
 4 particles or some threat, right?
 5 MS. AHERN: Objection to form.
 6 Q. Is that a fair statement of
 7 what macrophages do?
 8 A. Well, you know, the point that
 9 I'm making is that in many tumors, including
 10 ovary, you find macrophages. They're not
 11 there engulfing any foreign particle.
 12 They're being attracted by the malignant
 13 epithelial cells. This is part of the
 14 problem with the interaction of the stroma to
 15 the epithelium. They're coming into the
 16 tumor; they're secreting more factors to make
 17 the tumor grow bigger. They're part of the
 18 tumor.
 19 So I don't see -- I don't think
 20 it's fair to say that those macrophages are
 21 there because of the foreign body. No. The
 22 macrophage may be there just because of the
 23 cancer, and then the foreign body came from

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1 something. It could be a contaminant.
 2 Q. Okay. I think we're talking
 3 about two different things. You agree that a
 4 macrophage -- I'm sorry. Strike that.
 5 You would agree that a
 6 macrophage's response is in some measure
 7 determined by the size of the foreign
 8 particle -- foreign body reaction, right?
 9 MS. AHERN: Objection to form.
 10 BY MR. DEARING:
 11 Q. In other words, if the particle
 12 was large, you would expect to see a giant
 13 cell, not a macrophage trying to sequester a
 14 particle?
 15 MS. AHERN: Objection to form.
 16 A. I'm not sure I agree with that
 17 either. I mean, again, one of the concepts
 18 is -- you know, for instance, TB. TB is a
 19 pretty big bacterium. That gets engulfed by
 20 a macrophage. So big particles can be
 21 engulfed by a macrophage. They can't digest
 22 it, so that creates a granuloma. They just
 23 sort of sit there.

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1 But -- I don't know if that
 2 answers your question.
 3 Q. Well, it sort of does, because
 4 I'm circling back to where I started. And
 5 that is, the macrophage activity, the
 6 macrophage's attempt to sequester a particle,
 7 digest a particle, even move to a particle,
 8 all of that stops when the tissue is removed
 9 from the body, right? The activity ceases?
 10 A. Well, the cells are dead.
 11 Q. Right. They all die when it's
 12 removed from the body.
 13 A. Yes.
 14 Q. That's where I was trying to
 15 get back to. You're taking me deeper than I
 16 want to go.
 17 A. I agree on that. Yeah. There
 18 isn't life after removal.
 19 Q. None of the opinions you've
 20 expressed today about talc and ovarian cancer
 21 have ever been peer reviewed, have they?
 22 A. No.
 23 Q. You agree that the papillary

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1 serous cancer that Ms. Brower had is the most
 2 likely histological type of cancer to recur?
 3 A. If you're talking total, if you
 4 look at recurrent ovarian cancers, are most
 5 of them pap serous, the answer is yes. Stage
 6 for stage. If you look at the stage III
 7 or IV clear cell, the chance of that
 8 recurring is just as high. But they're not
 9 common tumors.
 10 Q. Sure. Would you agree that
 11 papillary serous is the more aggressive of
 12 the four main histological subtypes of
 13 ovarian cancers?
 14 MS. AHERN: Objection to form.
 15 A. The pap serous tumors present
 16 at an advanced stage much more frequently. I
 17 think that contributes to its aggressiveness.
 18 Q. And so that makes them more
 19 likely to metastasize?
 20 A. That means they are
 21 metastasized at diagnosis.
 22 Q. You mentioned, when we were
 23 talking about talc contamination, that it's

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1 possible contamination occurred from a
2 previous surgery. Did you say something like
3 that?
4 A. I left it at the OR, path
5 suite, lab.
6 Q. The OR, when you say -- are you
7 referring to the ovarian cancer surgery?
8 A. Correct. So as you know,
9 surgeon cuts it out, it doesn't just,
10 unfortunately, miraculously show up in the
11 path suite. It gets puts onto a plate,
12 sometimes it sits there for a half hour to an
13 hour, because the surgeon is busy. Multiple
14 people touch it. You know, it's not -- and I
15 know this because part of the -- we get some
16 of our tumors from the OR. When we put them
17 in a culture, they're all contaminated with
18 bacteria. So it's not as clean of a process
19 as you would think it would be.
20 Q. Are you seeing talc in those?
21 A. I can't say I saw talc, no.
22 Q. And, of course, surgical gloves
23 haven't been dusted with talc in decades,

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1 right?
2 MS. AHERN: Objection to form.
3 A. Yes.
4 Q. And that's precisely why
5 surgical gloves are no longer dusted with
6 talc, because leaving traces of talc in the
7 peritoneal cavity can cause problems,
8 infections, foreign-body responses that can
9 affect a patient's health, right?
10 MS. AHERN: Objection to form.
11 A. There were some observations
12 that there was irritation, yeah, and
13 problems. Yeah.
14 Q. You agree that smoking, and
15 maybe in this case, secondhand smoke is not a
16 risk factor for papillary serous ovarian
17 cancer, right?
18 A. I don't know of any data that
19 supports that.
20 Q. We had two negatives going
21 there at the same time. Let me ask it a
22 different way.
23 Would you agree with me that

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1 cigarette smoke and secondhand cigarette
2 smoke exposure does not increase a woman's
3 risk of ovarian cancer?
4 A. Correct.
5 Q. Would you agree that obesity
6 does not increase a woman's risk of ovarian
7 cancer?
8 A. So, as you probably know, there
9 are some epidemiologic data to suggest that
10 obesity is a risk factor for ovarian cancer.
11 I don't -- I don't find that compelling. If
12 it is, it's a pretty weak one. This
13 particular patient, though, had a BMI that
14 was quite high.
15 Q. And that seems to be the way
16 the pendulum is swinging right now, is that
17 obesity has very little to do with a person's
18 predisposition for ovarian cancer?
19 A. It's much more for endometrial
20 cancer and breast cancer.
21 Q. Let me try to make a clear
22 record on that question. I babbled a little
23 bit.

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1 Would you agree with me that
2 obesity did not contribute to Ms. Brower's
3 ovarian cancer?
4 A. I think it's unlikely.
5 Q. Okay. You said that you treat
6 patients now and have most of your career.
7 What specific type of treatment do you offer
8 patients at this time in your career? I
9 mean, is it mostly consulting? Is it actual
10 treatment? What do you do?
11 A. So, again, most of my patients
12 have ovarian cancer. Most of the them are
13 going to be advanced stage -- excuse me --
14 initial diagnosis, in which case I'll
15 recommend surgery. I don't do the surgery.
16 Surgeons would the surgery, followed by
17 chemotherapy.
18 And many of my patients are
19 recurrent, so they'll come to me for a second
20 opinion if it's standard of care, which
21 sometimes it is, and they're coming from a
22 far distance, I'll say, it's not worth
23 traveling to Birmingham to get standard of

<p style="text-align: right;">Page 113</p> <p>1 care; get it locally. We'll communicate that 2 with a local doc. 3 If it's a unique treatment here 4 and/or clinical trial, then we'll treat them 5 and I'll guide that therapy. 6 Q. If you're recommending a 7 chemotherapeutic agent for a patient, do you 8 have a face-to-face discussion with them 9 about the risks and benefits of what you're 10 recommending? 11 A. Of course, yeah. 12 Q. And that's so the patient can 13 make an informed decision about what they put 14 in their body? 15 A. Correct. And they have to be, 16 of course, consented, both for standard of 17 care and clinical trial. 18 Q. I'm almost finished. The 19 opinions you've shared today about talc and 20 ovarian cancer, are they opinions that you've 21 held for years or is it just something you 22 started looking at in the past couple of 23 years when you got involved in this</p>	<p style="text-align: right;">Page 115</p> <p>1 Oncology. These are the big meetings. We 2 just got back from Kyoto IGCS. Talc and 3 ovarian cancer is never discussed. 4 Q. You would agree that you do 5 have some colleagues here at UAB that believe 6 that perineal talc exposure does increase a 7 woman's risk of ovarian cancer, right? 8 A. I certainly have never 9 discussed it with them. 10 Q. So are you saying you don't 11 know whether you have colleagues that believe 12 that, or you know that they exist, you just 13 haven't discussed it with them? 14 A. No. From my perspective, I 15 know of nobody here who has brought this 16 issue up to me or discussed it in a seminar. 17 Q. Some of them have published on 18 it. Are you aware of that? 19 A. Some of them have published on 20 it. This is within GYN/ONC or medical 21 oncology? 22 Q. Well, I'm not sure. But I can 23 tell you that the topic was perineal talc</p>
<p style="text-align: right;">Page 114</p> <p>1 litigation? 2 A. So I would say, essentially, 3 for years. We went through this a little bit 4 last time, which is in my own practice, but I 5 think all my colleagues, and we see patients 6 with ovarian cancer, talc doesn't come up as 7 a risk factor so we don't -- because we don't 8 essentially think there's substantial data. 9 So I've held that for a long time. And then 10 probably because of the litigation, have dug 11 down a little bit more into the epidemiologic 12 studies. 13 Q. So are you saying that you are 14 speaking today on behalf of all the 15 gynecologic oncologists at UAB, that none of 16 them believe that talc contributes to causing 17 ovarian cancer? 18 MS. AHERN: Objection to form. 19 A. I'm just sort of reflecting 20 what I think about the field. You know, I 21 meet all of these people -- and it goes way 22 beyond UAB -- at the Society of Gynecologic 23 Oncology, at American Society of Clinical</p>	<p style="text-align: right;">Page 116</p> <p>1 exposure and ovarian cancer. So there are 2 some oncologists within the UAB system that 3 have opinions that perineal talc exposure 4 does increase a woman's risk of ovarian 5 cancer. Are you aware of that? 6 A. I'm not aware of a specific 7 physician. 8 MR. DEARING: Okay. I think 9 that's all I have. 10 MS. FOSTER: I don't have any 11 questions. 12 EXAMINATION 13 BY MS. AHERN: 14 Q. I have just a couple of little 15 clarifications. 16 Doctor, earlier, you were asked 17 whether you considered macrophage activity as 18 a foreign body reaction, and I believe you 19 said yes. And I guess my question is -- I 20 think this may have been clarified toward the 21 end of the deposition, your exchange on 22 granulomas. But did you mean to suggest that 23 if you see macrophages, that you're seeing a</p>

<p style="text-align: right;">Page 117</p> <p>1 foreign-body response?</p> <p>2 A. Well, I didn't want to get down</p> <p>3 in the weeds on that, because, you know, I</p> <p>4 think macrophages do a lot of things. So I</p> <p>5 think if you look at a granuloma, which is a</p> <p>6 foreign body reacting to macrophages, that a</p> <p>7 macrophage is doing something. We now know</p> <p>8 that macrophages are seen in essentially all</p> <p>9 human tumors doing something completely</p> <p>10 different, and that's not a foreign-body</p> <p>11 reaction. So it's a mixed -- it's a little</p> <p>12 bit like what we get into when we hear the</p> <p>13 term "inflammation." This is a incredibly</p> <p>14 broad term that we need to be a little bit</p> <p>15 more scientifically specific.</p> <p>16 Q. Okay. So in other words,</p> <p>17 macrophages are not synonymous with</p> <p>18 foreign-body reactions or granulomas?</p> <p>19 A. No. They do lots of things.</p> <p>20 Q. And just going quickly back</p> <p>21 over some questions asked specifically about</p> <p>22 Mrs. Brower. And I know you don't have the</p> <p>23 medical records in front of you. But if I</p>	<p style="text-align: right;">Page 119</p> <p>1 breast cancer, so it does raise an issue</p> <p>2 about potential genetic predisposition for</p> <p>3 this disease.</p> <p>4 MS. AHERN: Okay. That's all I</p> <p>5 have.</p> <p>6 EXAMINATION</p> <p>7 BY MR. DEARING:</p> <p>8 Q. Do you know anything about the</p> <p>9 social history of those aunts, whether they</p> <p>10 were smokers or drinkers?</p> <p>11 A. I don't think there was</p> <p>12 anything listed in the counseling note.</p> <p>13 Q. Would you agree that women who</p> <p>14 drink alcohol are at an increased risk of</p> <p>15 breast cancer?</p> <p>16 A. It's, I think, fairly</p> <p>17 substantial data to link some alcohol</p> <p>18 ingestion to breast cancer. Yes. It's also</p> <p>19 a common disease, unfortunately.</p> <p>20 Q. Do you agree that tumor cells</p> <p>21 themselves can cause a foreign-body-type</p> <p>22 reaction, like a giant cell could respond to,</p> <p>23 you know, grow tumor cells, cancer cells?</p>
<p style="text-align: right;">Page 118</p> <p>1 represent that Northside Medical records put</p> <p>2 her age of menarche at 10 and menopause at</p> <p>3 57, is that consistent with your general</p> <p>4 recollection of your review?</p> <p>5 A. Yes.</p> <p>6 Q. Is that also consistent -- in</p> <p>7 your opinion, would that be a longer than</p> <p>8 average ovulatory period?</p> <p>9 A. Yes.</p> <p>10 Q. And you were asked some</p> <p>11 questions about and you discussed her family</p> <p>12 history, and I think you had the opportunity</p> <p>13 to review the genetic counseling record. And</p> <p>14 one of the things you mentioned you had</p> <p>15 forgotten was that she had six maternal aunts</p> <p>16 who had had breast cancer. Is that</p> <p>17 significant in any way to Mrs. Brower's</p> <p>18 family history?</p> <p>19 A. Well, it's notable. We went</p> <p>20 over it before. I think as you get a little</p> <p>21 bit further away from first-degree relatives,</p> <p>22 it becomes less of an impact. But we're</p> <p>23 talking about a lot of maternal aunts with</p>	<p style="text-align: right;">Page 120</p> <p>1 A. That's a hard one to answer. I</p> <p>2 mean, a lot of times, tumors are described as</p> <p>3 a wound that doesn't heal. Is that a</p> <p>4 foreign-body reaction? That's something</p> <p>5 different. You can find giant cells within</p> <p>6 tumors. Do we know exactly what they're</p> <p>7 doing? I don't know.</p> <p>8 Q. Can cancer cells or tumors</p> <p>9 invoke a granulomatous response?</p> <p>10 MS. AHERN: Objection to form.</p> <p>11 A. That's an interesting question.</p> <p>12 I certainly don't -- it's not common, and I'm</p> <p>13 trying to think of a cancer where I would see</p> <p>14 a granulomatous response. It's not coming to</p> <p>15 mind.</p> <p>16 MR. DEARING: Okay. I think</p> <p>17 that's it. Doctor, thank you for</p> <p>18 your time.</p> <p>19 (The deposition of MICHAEL</p> <p>20 BIRRER, M.D., concluded at</p> <p>21 11:05 a.m.)</p> <p>22 * * * * *</p> <p>23</p>

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Commissioner for the
State of Alabama at Large
CCR EXPIRATION: 9/30/19
MY COMMISSION EXPIRES: 5/17/21

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Exhibit 44

REPORTS

Prospective Study of Talc Use and Ovarian Cancer

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Background: Perineal talc use has been associated with an increased risk of ovarian cancer in a number of case-control studies; however, this association remains controversial because of limited supporting biologic evidence and the potential for recall bias or selection bias in case-control studies. In this study, we conducted a prospective analysis of perineal talc use and the risk of ovarian cancer. **Methods:** The Nurses' Health Study is a prospective study of 121 700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. Talc use was ascertained in 1982 by use of a self-administered questionnaire: after exclusions, 78 630 women formed the cohort for analysis. Three hundred seven epithelial ovarian cancers subsequently diagnosed in this cohort through June 1, 1996, were confirmed by medical record review and met inclusion criteria. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs). **Results:** In 1982, 40.4% ($n = 31\,789$) of the cohort reported ever using talc, and 14.5% ($n = 11\,411$) reported ever using talc daily. We observed no overall association with ever talc use and epithelial ovarian cancer (multivariate RR = 1.09; 95% CI = 0.86–1.37) and no increase in risk of ovarian cancer with increasing frequency of use. There was a modest elevation in risk for ever talc use and invasive serous ovarian cancer (multivariate RR = 1.40; 95% CI = 1.02–1.91). The risk of epithelial ovarian cancer for talc users was not greater among women who had never had a tubal ligation (multivariate RR = 0.97; 95% CI = 0.71–1.32). **Conclusion:** Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk

overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer. [J Natl Cancer Inst 2000;92:249–52]

Talc was originally implicated as a possible ovarian carcinogen because of its chemical similarity to asbestos, which has been linked to ovarian cancer in occupational settings and is associated with mesotheliomas histologically resembling epithelial ovarian cancers (1–3). Perineal use of talcum powder has been positively associated with ovarian cancer risk in a number of case-control studies (4–13), although the magnitude of the associations has been modest, with odds ratios ranging from 1.2 to 1.9, and not all results reached statistical significance (5,6,8). Despite this relative consistency among studies, the limited supporting biologic evidence, together with the possibility of recall and selection bias in case-control studies (1), has raised questions about the plausibility of the association. We, therefore, prospectively examined the relationship between perineal talc use and ovarian cancer risk in a large cohort of U.S. women.

METHODS

The Nurses' Health Study, established in 1976, is a prospective cohort of 121 700 registered nurses living in 11 of the larger states in the United States. Questionnaires were mailed to married, female nurses aged 30–55 years, requesting information on health-related issues, including medical history and potential risk factors for cancer. Follow-up questionnaires have been mailed every 2 years to update information on exposures and to ascertain newly diagnosed diseases. The study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, MA.

Ascertainment of cases. We sought medical records from all women who reported a diagnosis of ovarian cancer or who were deceased in each follow-up cycle. Records were reviewed by physicians unaware of exposure status. Histologic subtypes were determined from pathology reports, and epithelial ovarian cancers were classified as serous cancers (including cystadenocarcinoma and papillary adenocarcinoma), mucinous cancers (including adenocarcinoma and mucinous papillary adenocarcinoma), and endometrioid cancers (clear cell and other types, including mixed epithelial tumors). Borderline histologic tumors are included in the analysis. Deaths are reported by relatives and postal authorities, as well as a search of the National Death Index. Mortality follow-up is estimated to be 98% complete in this cohort (14). Cases of epithelial ovarian cancer (International Classification of Diseases Code, ICD183.0), confirmed by medical rec-

ord review or death certificate, occurring between the return of the 1982 questionnaire and June 1, 1996, were included in the analysis.

Exclusions. Women who did not respond to the question on talc use in 1982 were excluded from this analysis. We also excluded women who had reported a diagnosis of cancer (other than nonmelanoma skin cancer) before 1982, as well as women who reported bilateral oophorectomy, surgery with an unknown number of ovaries removed, and a history of radiation therapy. Validity of self-reported surgical menopause has been assessed previously, and agreement with medical records was more than 97% (15). These exclusions were updated every 2 years. At baseline, 78 630 women were eligible for the analysis. The resulting population after exclusions contributed 984 212 person-years of follow-up and 307 cases of epithelial ovarian cancer.

Ascertainment of talc exposure. Use of talcum powder was ascertained on the 1982 questionnaire in the following ways: "Have you ever commonly used talcum, baby powder, or deodorizing powder *a*) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or *b*) to apply on sanitary napkins? No, Yes." We classified "ever talc use" as ever talc use on either the perineal area or sanitary napkins.

Other covariates. Potential risk factors and confounders of the association between ovarian cancer and exposures of interest in this analysis also were obtained from the biennial questionnaires and were updated every 2 years where relevant. Oral contraceptive use was asked every 2 years from 1976 through 1982, by which time use was rare. Tubal ligation history was asked as part of a question on methods of contraception from 1976 through 1984, and, in 1994, women were asked if they had ever

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See "Notes" following "References."

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had a tubal ligation and, if so, at what age. Family history of ovarian cancer was not asked until 1992. Parity was defined as the number of pregnancies lasting 6 months or more and was asked through 1984.

Statistical analysis. Incidence rates (number of cases for each category of exposure divided by person months of follow-up in that cycle) were calculated for each category, adjusting for age in 5-year intervals. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs) of disease for each exposure category (16). For age-adjusted analyses, we categorized variables as follows: parity (0, 1–2, or ≥ 3), oral contraceptive use (never, past, or current), tubal ligation (yes or no), postmenopausal hormone use (never, past, or current), cigarette smoking (never, past, or current), and body mass index, i.e., weight in kilograms/height in meters squared (<21 , 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥ 29 kg/m²). In multivariate analyses, we adjusted for age (years) and for potential risk factors by use of indicator variables for each category as described above, except for parity (0, 1–2, 3–4, or ≥ 5) and duration of oral contraceptive use (never or <3 , 3–5, or >5 years), for which we used a larger number of categories to more appropriately control for confounding. In addition we controlled for age at menarche, duration of breast-feeding, and age at menopause. However, since this did not alter the estimates for talc use, further models did not control for these variables. Body mass index and duration of oral contraceptive use were also entered as continuous variables, and similar estimates were obtained. All RRs reported are multivariate unless otherwise stated. *P* values reported are two-sided.

RESULTS

Three hundred seven women developed ovarian cancer in the cohort from 1982 through 1996 who responded to the 1982 questionnaire on talc use. In 1982, 40.4% ($n = 31\,789$) of the baseline cohort reported ever using talc, of which 14.5% ($n = 11\,411$) were ever daily talc users. Talc use was associated with higher body mass index and inversely associated with current cigarette smoking (Table 1).

We did not observe an overall association with ever use of talc and epithelial ovarian cancer (RR = 1.09; 95% CI = 0.86–1.37). There was also no elevation in risk among daily users of perineal talc, and no trend was seen with increasing frequency of use (Table 2). Talc use on sanitary napkins was inversely related to ovarian cancer, but the association was statistically nonsignificant. Exclusion of use of talc on sanitary napkins from the ever use of talc variable did not substantially alter the results. We also evaluated the risk for women who used both perineal talc and talc on sanitary napkins but did not see an effect compared with never users of talc (RR = 0.90; 95% CI = 0.59–1.37).

When we stratified by histologic sub-

Table 1. Age-standardized prevalence of ovarian cancer risk factors according to perineal talc use in 1982*

	Ever perineal talc use, % [†] ($n = 31\,789$)	No perineal talc use, % ($n = 46\,841$)
Parity		
0	6.3	6.4
1–2	35.0	35.2
≥ 3	58.7	58.4
Oral contraceptive use		
Current	0.5	0.6
Past	49.2	49.8
Never	50.4	49.6
Hormone use, postmenopausal women only		
Current	12.1	12.9
Past	20.5	20.4
Never	67.4	66.7
Tubal ligation, yes	17.6	17.6
Cigarette smoking		
Never	44.9	43.2
Past	30.3	28.3
Current	24.9	28.5
Body mass index quintiles, kg/m ²		
<21.0	16.0	22.1
21.0–22.9	20.9	25.4
23.0–24.9	20.1	20.6
25.0–28.9	22.8	19.6
≥ 29	19.8	12.0

*Numbers do not always add up to 100% because of missing data or rounding.

[†]Ever talc use coded as either talc use on perineal area or talc use on sanitary napkins.

Table 2. Talc use and ovarian cancer: 1982 through 1996 (all subtypes included)*

	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR [†] (95% CI)
Talc use on perineum				
Never	186	608 020	1.0 (referent)	1.0 (referent)
<1 /wk	43	128 923	1.10 (0.79–1.53)	1.14 (0.81–1.59)
1–6/wk	30	105 186	0.95 (0.65–1.40)	0.99 (0.67–1.46)
Daily	48	142 083	1.09 (0.79–1.49)	1.12 (0.82–1.55)
Talc use on sanitary napkins				
No	242	781 421	1.0 (referent)	1.0 (referent)
Yes	32	111 399	0.89 (0.62–1.29)	0.89 (0.61–1.28)
Ever perineal talc use				
No	179	586 758	1.0 (referent)	1.0 (referent)
Yes	128	397 454	1.05 (0.84–1.32)	1.09 (0.86–1.37)
Talc use, perineal and sanitary napkins				
None	179	586 758	1.0 (referent)	1.0 (referent)
Either talc use on perineum or use on sanitary napkins	103	307 317	1.11 (0.87–1.41)	1.15 (0.90–1.46)
Use on both sanitary napkins and perineum	25	90 137	0.89 (0.58–1.35)	0.90 (0.59–1.37)

*RR = relative risk; CI = confidence interval.

[†]Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ≥ 5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21 , 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥ 29 kg/m²), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

type, we observed a modest increase in risk for ever talc use for serous invasive cancers (RR = 1.40; 95% CI = 1.02–1.91) but not for all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers (Table 3). For women who reported ever daily use

of talc, the RR of invasive serous cancer was 1.49 (95% CI = 0.98–2.26). The RRs for ever talc users of less than once per week and one to six times per week were 1.29 (95% CI = 0.81–2.04) and 1.49 (95% CI = 0.77–2.11), respectively (*P* for trend = .05).

Table 3. Talc use and ovarian cancer: 1982–1996 (by histologic subtype)*

Histologic subtype	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
All serous cancers, ever perineal talc use				
No	101	586 771	1.0 (referent)	1.0 (referent)
Yes	84	397 459	1.23 (0.92–1.64)	1.26 (0.94–1.69)‡
Serous invasive cancers, ever perineal talc use				
No	84	586 771	1.0 (referent)	1.0 (referent)
Yes	76	397 459	1.33 (0.98–1.82)	1.40 (1.02–1.91)‡
Endometrioid cancers, ever perineal talc use				
No	26	586 771	1.0 (referent)	1.0 (referent)
Yes	16	397 459	0.91 (0.49–1.69)	0.91 (0.49–1.87)
Mucinous cancers, ever perineal talc use				
No	30	586 771	1.0 (referent)	1.0 (referent)
Yes	20	397 459	0.98 (0.56–1.73)	0.93 (0.53–1.66)

*RR = relative risk; CI = confidence interval.

†Multivariate analyses controlling for age (years), parity (0, 1–2, or ≥ 3), oral contraceptive use (never or ever), and tubal ligation history (yes or no).

‡Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ≥ 5), duration of oral contraceptive use (never or < 3 y, 3–5 y, or > 5 y), body mass index (body weight in kilograms/height in meters squared: < 21 , 21.0–22.9, 23.0–24.9, 25.0–28.9, or ≥ 29 kg/m²), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Because the talc hypothesis depends on the ability of fibers to migrate up a patent genital tract to the ovaries, we evaluated the risk among women who had reported a tubal ligation and those who had not. Women who were ever talc users and had never had a tubal ligation were not at increased risk of epithelial ovarian cancer compared with women who had not used talc (RR = 0.97; 95% CI = 0.71–1.32). There was no evidence of heterogeneity of RRs between women who had a tubal ligation and women who did not. In addition, when women who had had a tubal ligation or simple hysterectomy were excluded from the analysis, the RR for ever talc use was 1.15 (95% CI = 0.89–1.49). For serous invasive cancers, the RR for women who had never had a tubal ligation was similar to that for women without a tubal ligation; however, the number of case patients who had had a tubal ligation was small (data not shown).

Cosmetic talc may have been more likely to contain asbestos fibers prior to 1976, before voluntary guidelines were proposed (9). As a proxy for early talc use, we assessed risk among women 45 years old or older in 1982. There was no evidence that older women in 1982 were at greater risk of ovarian cancer overall; the RR for ever talc use compared with never talc use for women under 45 years was 0.95 (95% CI = 0.59–1.53) and among women 45 years old or older was 1.13 (95% CI = 0.86–1.47). However, women 45 years old or older in 1982 who

ever used talc had a higher risk of serous invasive cancer (RR = 1.51; 95% CI = 1.07–2.15). There was no evidence of effect modification by oral contraceptive use, body mass index, or cigarette smoking for epithelial cancers overall.

DISCUSSION

To our knowledge, this is the first prospective analysis of talc use and ovarian cancer, and it addresses some of the potential limitations of previous case-control studies. Because we ascertained talc exposure prior to case diagnosis, the possibility for recall bias, which has been raised as a potential explanation for previous positive findings in case-control studies (1), is eliminated, and selection bias is reduced. We controlled for known or suspected ovarian cancer risk factors in the analysis, such as parity, oral contraceptive use, tubal ligation history, and body mass index, reducing the potential for uncontrolled confounding.

However, there are several important limitations to our study. The questions on talcum powder use referred to ever use, and we cannot determine the age at which women began using talc or the duration of use. Thus, we were unable to assess the potential effect of talc use before first pregnancy, which has been shown to be a stronger risk factor for ovarian cancer than use after pregnancy in one study (13). The number of lifetime applications of talc has also been associated with increased risk of ovarian cancer in some

previous studies (9,13). Our relatively short follow-up period may be inadequate to detect an association if the latency for development of ovarian cancer is more than 15 years. Although we controlled for tubal ligation history, the tubal ligation question was asked as part of a question on contraceptive use; therefore, postmenopausal women and some premenopausal women who were not sexually active may not have responded to the question. Substantial residual confounding is unlikely, since there was no overall association between talc use and tubal ligation in this study. In addition, we excluded women who were postmenopausal in 1976 from analyses stratified by tubal ligation history. Finally, the prevalence of talc use in our study is somewhat higher than that in other studies and may reflect the fact that we asked about frequency of ever use rather than current regular use; this may have contributed to an attenuation of risk due to misclassification of exposure.

The potential effect of talc on the ovaries depends on migration of talc fibers through a patent genital tract, and we would, therefore, expect a stronger association among women without a tubal ligation who had used talc. However, no effect modification was seen by history of tubal ligation. Because we did not have the date of tubal ligation, some women may have begun talc use only after tubal ligation, potentially resulting in misclassification of talc use and attenuation of the RRs.

Since the first study showing an almost twofold increase in risk of ovarian cancer with any perineal talc use (4), most case-control studies have demonstrated positive associations with talc use (4–13), although not all have been statistically significant (5,6,8). Several studies (9,17–20) found no overall association between any genital talc use and ovarian cancer. We did not observe a dose-response relationship with talc use, and previous studies also have been inconsistent in this regard. Some studies (9,13,17) have demonstrated statistically insignificant trends in risk with increased frequency of talc use, duration of use, and measures of “total lifetime applications,” while other studies (6,8) have not observed a statistically significant dose response.

With regard to histologic subtypes, a recent study by Cramer et al. (13) observed the greatest risk for talc use and invasive serous cancer; however, other

studies found increased risks for endometrial cancers (9,12), serous cancers (7), and invasive cancers of all subtypes (12). Since serous cancers, which account for more than half of all invasive ovarian cancers, most resemble mesotheliomas, it could be hypothesized that this subtype may be most likely associated with talc use. In our stratification by subtype, we did observe a modest positive association with serous invasive cancers and ever talc use as well as a borderline significant trend for increasing frequency of ever use.

The biologic evidence for the association of talc and ovarian cancer is incomplete. Asbestos has been linked to ovarian cancer in occupational settings and is associated with peritoneal tumors similar to ovarian cancer (2,3,21). Because of the chemical similarity of talc and asbestos, talc also has been implicated as a possible ovarian carcinogen. Talc is able to migrate through the genital tract and gain access to the ovaries because talc fibers have been detected in benign and malignant ovarian tissue (22), although no relation between reported levels of talc exposure and ovarian talc counts has been observed (23). There have been few studies (24,25) of talc exposure in animals, and these studies have not demonstrated an increase in ovarian cancer among animals subjected to chronic talc exposure. These data should be interpreted cautiously because there are important anatomic and physiologic differences between rodents and humans, and talc in animals is often administered at high dose via aerosol exposure (24).

In summary, we did not observe an overall association between epithelial ovarian cancer and ever use of talc, and there was no apparent dose response, although we lacked information on duration of talc use. In analyses stratified by histologic subtype, we observed a modest positive association between invasive serous cancer and ever talc use. Our results provide little support for any substantial association between perineal talc use and

ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancers.

REFERENCES

- (1) Harlow BL, Hartge PA. A review of perineal talc exposure and risk of ovarian cancer. *Regul Toxicol Pharmacol* 1995;21:254-60.
- (2) Keal E. Asbestosis and abdominal neoplasms. *Lancet* 1960;2:1211-6.
- (3) Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40 year follow-up. *Br J Indust Med* 1982;39:344-8.
- (4) Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer* 1982;50:372-6.
- (5) Chen Y, Wu PC, Lang JH, Ge WY, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol* 1992;21:23-9.
- (6) Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles DL, Kampert JB, Grosser S, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol* 1988;128:1228-40.
- (7) Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol* 1997;145:459-65.
- (8) Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer* 1989;60:592-8.
- (9) Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* 1992;80:19-26.
- (10) Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. *Int J Cancer* 1995;62:678-84.
- (11) Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker J. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil Steril* 1996;65:13-8.
- (12) Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. *Cancer* 1997;79:2396-401.
- (13) Cramer DW, Liberman RE, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer* 1999;81:351-6.
- (14) Stampfer MJ, Willett WC, Speizer FE, Sysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. *Am J Epidemiol* 1984;119:837-9.
- (15) Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. *JAMA* 1993;270:2813-8.
- (16) D'Agostino RB, Lee ML, Balanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med* 1990;9:1501-15.
- (17) Hartge P, Hoover R, Leshner LP, McGowan L. Talc and ovarian cancer [letter]. *JAMA* 1983;250:1844.
- (18) Rosenblatt KA, Thomas DB. Lactation and the risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Epidemiol* 1993;22:192-7.
- (19) Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer* 1993;55:508-10.
- (20) Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol* 1999;93:372-6.
- (21) Wignall BK, Fox AJ. Mortality of female gas mask assemblers. *Br J Indust Med* 1982;39:34-8.
- (22) Henderson WJ, Joslin CC, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. *J Obstet Gynecol* 1971;78:266-72.
- (23) Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol* 1996;174:1507-10.
- (24) Boorman GA, Seely JC. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. *Regul Toxicol Pharmacol* 1995;21:242-3.
- (25) Hamilton TC, Fox H, Buckley CH, Henderson WJ, Griffiths K. Effects of talc on the rat ovary. *Br J Exp Pathol* 1984;65:101-6.

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Exhibit 45

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GENITAL TALC EXPOSURE AND RISK OF OVARIAN CANCER

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Epidemiologic studies have suggested an increased risk for ovarian cancer associated with the use of talcum powder in genital hygiene, but the biologic credibility of the association has been questioned. We conducted a population-based case-control study in eastern Massachusetts and New Hampshire involving 563 women with newly diagnosed epithelial ovarian cancer and 523 control women selected either by random digit dialing or through lists of residents. Use of body powders was assessed through personal interview and the exposure odds ratio (OR) for the use of talc in genital hygiene was calculated. Cases were more likely than controls (45% vs. 36%) to have used talc as a body powder in some manner, and the excess was confined to patients who used talc on the perineum directly or as a dusting powder to underwear or sanitary napkins. Relative to women who never used body powder or used it only in non-genital areas, the OR (and 95% confidence interval) associated with genital exposure to talc was 1.60 (1.18 and 2.15) after adjustment for age, study location, parity, oral contraceptive use, body mass index and family history of breast or ovarian cancer. Exposure prior to rather than after a first livebirth appeared to be more harmful, and the association was most apparent for women with invasive serous cancers and least apparent for those with mucinous tumors. We conclude that there is a significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer that, when viewed in perspective of published data on this association, warrants more formal public health warnings. *Int. J. Cancer* 81:351–356, 1999.

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An association between the use of talc in genital hygiene and ovarian cancer was first examined in an epidemiologic study in 1982 (Cramer *et al.*, 1982). An elevated odds ratio for genital talc exposure was observed in this study, in 8 of the largest subsequent epidemiological studies (Whittemore *et al.*, 1988; Booth *et al.*, 1989; Harlow *et al.*, 1992; Chen *et al.*, 1992; Purdie *et al.*, 1995; Shushan *et al.*, 1996; Cook *et al.*, 1997; Chang and Risch, 1997) and in a study of borderline tumors (Harlow and Weiss, 1989). Only 3 smaller studies reported a null association (Hartge *et al.*, 1983; Rosenblatt *et al.*, 1992; Tzonou *et al.*, 1993). Despite this consistency, the association is still viewed with skepticism based upon weak odds ratios, poor dose-response relationships and an incomplete understanding of the biological mechanism by which talc might lead to ovarian cancer. We have completed a large population-based case-control study of ovarian cancer which offers new perspectives on the validity of the talc and ovarian cancer association.

MATERIAL AND METHODS

We conducted a population-based case-control study of women with newly diagnosed ovarian cancer who resided in eastern Massachusetts (MA) or New Hampshire (NH). Women with ovarian cancer were identified through hospital tumor boards and statewide cancer registries. Between 5/92 and 3/97, 1,080 cases of ovarian cancer were identified. After excluding 203 cases who had died or moved, had no telephone, did not speak English or had a non-ovarian primary tumor after review, 877 women remained eligible. Physicians denied permission to contact 126 (14%) of these women, and 136 cases (16%) declined to participate. Our

analysis is based upon data from 563 cases with epithelial ovarian cancer, including those with tumors of borderline malignancy.

We identified control women using random digit dialing (RDD) in which the sampling unit for an interviewed case comprised the 99 telephone numbers generated from the first 5 digits of her telephone number plus all remaining combinations of the last 2 digits (excluding the case's own number). These numbers were listed in random order and called to screen households for potential controls who were within 4 years of the age of the case. Excluding business and non-working numbers, approximately 5,400 calls yielded 10% of households in which the household member declined to provide a household census and 80% of households in which an age and sex matched control for a case could not be made or a potential control was ineligible because of a prior oophorectomy. Of the remaining 10% of households screened with a potential eligible control, 72% agreed to participate. RDD proved inefficient for identifying controls over age 60 in MA since a substantially greater number of households needed to be screened to obtain an older control. Except in NH where complete listings of residents were unavailable, we chose to identify older controls in MA by randomly selecting women through use of lists (townbooks) of all residents in towns by name, age, and address according to precinct. We matched older controls to cases by community and age within 4 years based on the townbooks. Of 328 sampled townbook controls, 21% could not be reached, 18% were ineligible and 30% declined to participate. This analysis includes a total of 523 RDD and townbook controls.

In introducing the study to potential cases and controls, specific hypotheses including the talc association were not discussed. After written informed consent, we assessed demographic information, menstrual and reproductive history, medical and family history and personal habits using an in-person interview. We assessed exposures occurring prior to a "reference date," defined as 1 year before the date of diagnosis for cases and the date of interview for controls. We asked whether women had "regularly used talc, baby, or deodorizing powders dusted or sprayed" to feet, arms or other non-genital areas, to the genital or rectal area, on sanitary napkins, or on underwear, with the latter 3 methods defined as "genital exposure" and either no use or use in non-genital areas defined as "no genital exposure." A husband's use of powder in his genital area was also assessed. Age at first use, types of powder(s) used, applications per month and total years of use in genital hygiene were assessed in talc users. We did not assess potential talc exposure from diaphragms or condoms, exposures not found to be associated with ovarian cancer in our previous studies (Cramer *et al.*, 1982; Harlow *et al.*, 1992).

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TABLE I – PERINEAL TALC EXPOSURE¹ IN RELATION TO OVARIAN CANCER RISK BY CHARACTERISTICS OF STUDY PARTICIPANTS

	Cases		Controls		Age-adjusted ² OR	(95% C.I.)
	Total	Talc exposure (%)	Total	Talc exposure (%)		
Age						
<50	266	66 (24.8)	262	43 (16.4)	1.68	(1.09, 2.58)
≥50	297	86 (29.0)	261	52 (19.9)	1.64	(1.11, 2.43)
Study center						
MA	433	126 (29.1)	411	85 (20.7)	1.56	(1.14, 2.14)
NH	130	26 (20.0)	112	10 (8.9)	2.49	(1.14, 5.45)
Education						
≤12	218	58 (26.6)	171	28 (16.4)	1.79	(1.08, 2.97)
>12	344	93 (27.0)	352	67 (19.0)	1.59	(1.10, 2.27)
Marital status						
Never married	110	31 (28.2)	61	10 (16.4)	1.77	(0.78, 4.00)
Ever married	453	121 (26.7)	462	85 (18.4)	1.62	(1.18, 2.22)
Religion						
Jewish	54	18 (33.3)	44	10 (22.7)	1.69	(0.68, 4.18)
Non-Jewish	509	134 (26.3)	479	85 (17.8)	1.63	(1.20, 2.22)
Weight						
<140	237	57 (24.0)	247	40 (16.2)	1.60	(1.02, 2.53)
≥140	326	95 (29.1)	275	55 (20.0)	1.65	(1.13, 2.42)
Use of OCs (months)						
<3 or never	334	98 (29.3)	247	52 (21.0)	1.55	(1.06, 2.28)
≥3	229	54 (23.6)	276	43 (15.6)	1.67	(1.07, 2.61)
Number of liveborn children						
0	185	55 (29.7)	106	20 (18.9)	1.65	(0.92, 2.98)
1–2	212	49 (23.1)	209	34 (16.3)	1.56	(0.95, 2.54)
3+	166	48 (28.9)	208	41 (19.7)	1.69	(1.04, 2.75)
Prior tubal ligation						
No	488	135 (27.7)	437	76 (17.4)	1.80	(1.31, 2.47)
Yes	75	17 (22.7)	86	19 (22.1)	0.98	(0.46, 2.08)
Prior hysterectomy						
No	529	139 (26.3)	487	88 (18.1)	1.60	(1.18, 2.16)
Yes ³	34	13 (38.2)	36	7 (19.4)	2.61	(0.88, 7.78)
Family history of breast or ovarian cancer						
No	481	132 (27.4)	462	87 (18.8)	1.59	(1.17, 2.17)
Yes	82	20 (24.4)	61	8 (13.1)	2.21	(0.89, 5.48)

OR: odds ratio; CI: confidence interval; OCs: oral contraceptives.—¹Sources of perineal talc exposure include dusting of underwear, diaphragms, sanitary napkins and/or dusting of genital area.—²Adjusted for age as a continuous variable.—³Excludes those with tubal ligation prior to hysterectomy.

For all cases studied, we reviewed pathology reports and sought slides in any instance where there was a discrepancy between histologic description and final diagnosis. After completing the review, cases were grouped according to the following histologic categories: serous cancers (including serous cystadenocarcinomas and surface papillary carcinomas), mucinous cancers, endometrioid and clear cell cancers, including mixed mesodermal or mixed epithelial with an endometrioid or clear cell component) and undifferentiated or other cancers. According to Young *et al.* (1994), serous tumors tend to be either borderline or invasive and seldom display a mixture while borderline and invasive grades often intermingle within other histologic types, especially the mucinous tumors. Based on this tendency, only serous borderline tumors were distinguished from invasive cancers when considering odds ratios by histologic type and grade.

Since matching was performed as the most convenient means for selecting controls comparable to cases in age and geographic locale and not as the principal means of controlling for confounding, matching was not preserved in the analysis. We analyzed our data by constructing frequency counts of cases and controls by study variables and by calculating crude odds ratios (OR). We then used unconditional logistic regression to adjust for the matching variables including age (continuous), study site (MA, NH), body mass index (continuous), which might have influenced likelihood of using body powder, and for variables strongly linked to ovarian cancer risk such as parity (0, 1), oral contraceptive use (never or <3 months, ≥3 months) and family history of breast or ovarian cancer (no, yes) and tubal ligation (no, yes). Most analyses were

performed by using the SAS system (SAS Institute, Cary, NC). Tests for linear trend were performed using the likelihood ratio test with continuous forms of the talc variables. Frequency counts from studies included in our review of published studies were entered into STATA (College Station, TX) to compute crude and combined odds ratios.

RESULTS

Table I summarizes data regarding how cases and controls differed demographically and by known risk factors for ovarian cancer, how these same variables influenced genital talc exposure among controls and how the association between talc use in the genital area and ovarian cancer varied among strata. Controls were more likely than cases to have gone beyond high school, to have married, to have had children and to have used oral contraceptives. In examining the frequency of talc use among controls, only study location significantly influenced likelihood of genital talc exposure. Women from New Hampshire were less likely to have used talc in the genital area compared to women from Massachusetts. Ovarian cancer cases in almost all strata were more likely to have used powder genitally compared to controls, with corresponding elevated odds ratios. A notable exception was the lack of an association between talc use and ovarian cancer among women who reported having had a tubal ligation.

Table II shows adjusted odds ratios by manner, type and frequency of powder use. A greater percentage of cases had regularly used powder in some manner compared to the controls.

TABLE II – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH TYPES AND FREQUENCY OF POWDER USE

Type of personal use	Cases	Controls	Adjusted OR ¹	(95% C.I.)
	Number (%)	Number (%)		
No personal use	312 (55.4)	334 (63.9)	1.0	
Use, non-genital areas	99 (17.6)	94 (18.0)	1.08	(0.77, 1.50)
Use, dusting perineum	71 (12.6)	51 (9.8)	1.45	(0.97, 2.18)
Use, dusting sanitary napkin	20 (3.6)	12 (2.3)	1.45	(0.68, 3.09)
Use, dusting underwear	8 (1.4)	6 (1.2)	1.21	(0.40, 3.64)
Multiple uses genital area	53 (9.4)	26 (5.0)	2.15	(1.30, 3.57)
Genital use				
No personal genital exposure	411 (73.0)	428 (81.8)	1.0	
Any personal genital exposure	152 (27.0)	95 (18.2)	1.60	(1.18, 2.15)
Longest used type of powder ²				
No genital use	411 (73.4)	428 (81.8)	1.0	
Talc	148 (26.4)	92 (17.6)	1.69	(1.26, 2.27)
Cornstarch	1 (0.2)	3 (0.6)	0.31	(0.03, 3.01)
Husband use ^{3,1}				
No	291 (87.6)	346 (92.0)	1.0	
Yes	41 (12.4)	30 (8.00)	1.52	(0.92, 2.52)
Frequency of use per month ⁴				
<30	64 (11.5)	28 (5.4)	2.21	(1.37, 3.56)
30–39	59 (10.6)	51 (9.8)	1.17	(0.78, 1.76)
40+	23 (9.8)	15 (2.9)	1.57	(0.80, 3.10)

¹Adjusted for age (continuous), study center (MA, NH), tubal ligation (ever, never), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months), and primary relative with breast or ovarian cancer (yes, no) and other categories of genital talc use, except where noted. ²Adjusted for age (continuous), study center (MA, NH), and tubal ligation (ever, never) and other powder. ³Among married women with no personal genital talc use. ⁴Total of all uses in the genital area.

Relative to those with no use of a body powder, those who used powder only in non-genital areas did not have an increased risk of ovarian cancer [OR=1.08 (0.77 and 1.50)]. However, elevated ORs and (95% CI) were observed for women who directly powdered the genital or rectal area [1.45 (0.97 and 2.18)]; who dusted sanitary napkins: 1.45 (0.68 and 3.09); who dusted underwear [1.21 (0.40 and 3.64)] and who used powder in multiple ways in the genital area [2.15 (1.30 and 3.57)]. There was a significant excess of cases who regularly used powder in some manner in the genital area, and the adjusted OR was similar whether the non exposed referent group was considered to be women with no use of talc anywhere [OR= 1.58, (1.16 and 2.16)] or women with no genital use including those who used it as a body powder in non-genital areas [OR= 1.60 (1.18 and 2.15)]. Few of the women in our study reported use of cornstarch rather than a talc-based powder leading to an imprecise and non-significant OR for ovarian cancer risk associated with its use in the genital area. Among married women who never personally used talc in the genital area, there was an increase of borderline significance in ovarian cancer risk for women whose husbands had used talc in their genital area [OR= 1.52 (0.92, 2.52)]. When we examined all methods of genital talc use (except exposure from a husband), we found that most of those who used talc had 30 or more applications per month, but there was no apparent trend for increasing risk for ovarian cancer with increasing number of monthly applications.

Table III examines risk for ovarian cancer associated with ordinal categories related to duration or intensity of talc exposure in the genital area relative to women who never used talc or who used it only in non-genital areas. No clear linear trend was apparent in ORs for categories of age at first use, years of use or total applications. To examine dose response, each of these variables was used as a continuous variable in multivariate models. Linear trends were significant only in those models that included women who were not exposed. To duplicate an analysis performed in a previous report (Harlow *et al.*, 1992), we examined total applications censored by excluding use after closure of the female tract or during non-ovulatory years. Although the ORs for the categories displayed a trend, once again only the multivariate model including the non-genitally exposed revealed a significant trend.

Table IV presents a more detailed analysis of the effect of genital use of talc in women who had no pregnancies at all, in women who had a pregnancy not resulting in a liveborn and in women with a liveborn pregnancy. In the latter 2 groups, we examined risk for ovarian cancer with the timing of talc use in relation to the first pregnancy. Genital talc use that began after a first pregnancy appeared to be associated with lower risk compared to use which began before the first pregnancy. The effect was more apparent among those with a liveborn. Eighty-five of 374 parous cases used at least some talc prior to their first liveborn compared to 64 of 416 parous controls, leading to an adjusted OR (95% CI) of 1.58 (1.10 and 2.29). In contrast, 8 of 378 parous cases used talc only after their first livebirth compared to 10 of 417 parous controls, leading to an adjusted OR(95% CI) of 0.97 (0.38 and 2.50) for ovarian cancer associated with talc use after a first livebirth.

Table V shows the average age and use of genital talc for all controls and for cases by histologic type of ovarian cancer. Average age differed by histologic type but did not account for the differences in ORs. The odd ratio for genital talc use was greatest (and significant) for invasive serous tumors and less than 1 only for mucinous tumors (invasive and borderline combined) after adjustment for age and other covariates.

DISCUSSION

Consistent with four recent case-control studies of ovarian cancer (Purdie *et al.*, 1995, Sushan *et al.*, 1996, Cook *et al.*, 1997, Chang and Risch, 1997), our results demonstrate a significant association between the use of talc in genital hygiene and risk for ovarian cancer. In our discussion, we will examine whether this association satisfies traditional criteria for a causal association including consistency and strength of the association, potential biases, dose response and biological credibility.

Figure 1 summarizes data on risk for ovarian cancer with any genital use of talc from 14 case-control studies including this one. The combined odds ratio and 95% CI is 1.36 (1.24 and 1.49), which is statistically significant. Odds ratios deviating most from the pooled value were observed in the smaller studies, and the test for heterogeneity was not significant ($p=0.085$). Thus, the criteria for

TABLE III – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH GENITAL USE OF TALC

Type of exposure	Cases	Controls	Adjusted OR ¹	(95% C.I.)
	Number (%)	Number (%)		
No genital use	411 (73.0)	428 (81.8)	1.0	
Age at first use				
<20	97 (17.4)	67 (12.8)	1.46	(1.03, 2.07)
20–25	36 (6.5)	18 (3.4)	1.87	(1.03, 3.39)
>25	13 (2.3)	9 (1.7)	1.54	(0.64, 3.72)
<i>p</i> -value for linear trend is 0.504 excluding non-exposed.				
Years of use				
<20	55 (9.9)	31 (5.9)	1.86	(1.16, 3.00)
20–30	32 (5.8)	26 (5.0)	1.33	(0.76, 2.30)
>30	59 (10.6)	37 (7.1)	1.44	(0.91, 2.26)
<i>p</i> -value for linear trend is 0.477 excluding non-genitally exposed and 0.062 including non-genitally exposed.				
Total applications				
<3000	51 (9.2)	27 (5.2)	1.84	(1.12, 3.03)
3000–10,000	36 (6.5)	28 (5.4)	1.43	(0.84, 2.41)
>10,000	59 (10.6)	39 (7.5)	1.43	(0.92, 2.22)
<i>p</i> -value for linear trend is 0.164 excluding non-genitally exposed and 0.472 including non-genitally exposed.				
Applications censored ²				
<3000	59 (10.6)	41 (7.8)	1.54	(1.01, 2.35)
3000–10,000	51 (9.2)	31 (5.9)	1.72	(1.08, 2.76)
>10,000	36 (6.5)	20 (3.8)	1.80	(1.02, 3.18)
<i>p</i> -value for linear trend is 0.675 excluding non-genitally exposed and 0.022 including non-genitally exposed.				

¹Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no), parity (0, ≥1), OC use (<3 months, ≥3 months), tubal ligation, and other categories of genital talc use, except where noted. ²Excludes applications following hysterectomy or tubal ligation and applications during pregnancy and periods of OC use. Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no).

TABLE IV – EVER USE OF TALC IN THE GENITAL AREA IN RELATION TO PREGNANCY AND CHILDBIRTH

Group	Cases			Controls			Adjusted OR	95% C.I.
	Total	Number exposed	(%) exposed	Total	Number exposed	(%) exposed		
Nulligravid ¹	145	42	(29.0)	82	17	(20.7)	1.48	(0.76, 2.86)
Nulliparous ¹ prior to first pregnancy	40	13	(32.5)	24	3	(12.5)	2.80	(0.64, 12.20)
Nulliparous ¹ only after first pregnancy	40	2	(5.0)	24	1	(4.2)	1.24	(0.10, 15.32)
Parous ¹ prior to first livebirth	374	85	(22.7)	416	64	(15.4)	1.58	(1.10, 2.29)
Parous ² only after first livebirth	378	8	(2.12)	417	10	(2.40)	0.97	(0.38, 2.50)

¹Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no). ²Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no) and tubal ligation.

TABLE V – HISTORY OF GENITAL TALC USE AND ASSOCIATED ODDS RATIOS BY HISTOLOGIC TYPE AND GRADE

Histologic type/grade	Total	Average age	Any use of genital talc	No use of genital talc	Adjusted OR ¹	(95% CI)
Controls	523	49.3	95	428	1.0	
Histologic type/grade						
Serous borderline	86	41.8	23	63	1.38	(0.82, 2.31)
Serous invasive	229	54.5	72	157	1.70	(1.22, 2.39)
Mucinous	83	46.7	16	67	0.79	(0.44, 1.40)
Endometrioid/clear cell	130	53.9	31	99	1.04	(0.67, 1.61)
Undifferentiated	35	52.9	10	25	1.44	(0.67, 3.08)

¹Adjusted for age (continuous), study center (MA, NH), primary relative with breast or ovarian cancer (yes, no), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months) and tubal ligation (ever, never).

consistency of the association appear to be satisfied. A summary odds ratio of 1.36 suggests that between 10 and 11% of ovarian cancers in these populations are attributable to the genital use of talc depending upon whether the average control exposure of 36% or average case exposure of 43% is considered.

Despite the consistency noted above, the relatively weak odds ratios observed could reflect potential biases, especially recall and confounding. Recall bias is possible because talc exposure in these

studies is based on personal recollection. However, recall bias seems more likely to affect exposures that have occurred over a short term than those that have occurred over a long term. Since average duration of talc use exceeded 20 years in both cases and controls in our current study, genital talc exposure may be less likely to be subject to recall bias. Furthermore, if publicity regarding the association correlated with selective recall, one might expect a trend for cases from more recent studies to report higher

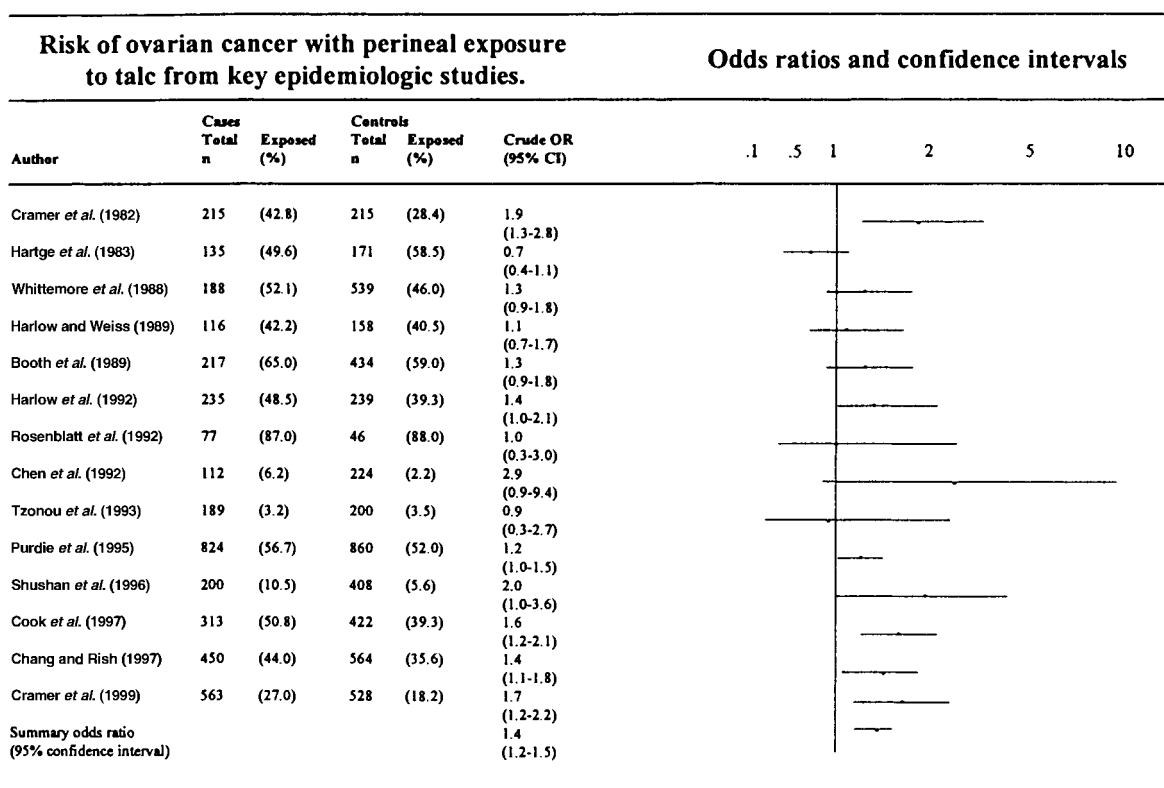


FIGURE 1 – Exposure rates, crude odds ratios and confidence intervals for case-control studies of genital talc use and ovarian cancer.

exposure rates, but the exposure rates noted in Figure 1 do not suggest this is the case. It also seems reasonable that selective recall would lead to cases reporting all types of talc exposure more frequently than controls, but our study found that cases did not report a significant excess of talc use in non-genital areas compared to controls. Finally, if recall accounted for the association, one would expect little variation in the odds ratios by histologic type of ovarian cancer which appears not to be the case from Table V. Our study found the greatest risk to be associated with invasive serous tumors, OR=1.70 (1.22 and 2.39). Cook *et al.* (1997) found talc use to be most strongly associated with serous and unclassified cancers, although Chang and Risch (1997) found endometrioid cancers to be more strongly linked with talc use.

Regarding potential bias from confounding, we found no evidence that genital talc exposure varied by key risk factors for ovarian cancer such as age, parity or OC use and little variability of the association by these and other variables (Table II). Chang and Risch (1997) adjusted for age, parity, breastfeeding, oral contraceptive use, tubal ligation or hysterectomy and family history and also found the association to persist. Characteristics such as body odor or excessive perspiration might represent subtle constitutional features that might predispose to both talc use and ovarian cancer, but adjusting for BMI should control for these effects. In addition, 2 previous studies (Cook *et al.*, 1997; Chang and Risch, 1997), and our current study found no evidence of elevated risk associated with genital use of a cornstarch based-powder, although in all of these studies the exposure was infrequent and the OR and confidence interval was wide. Further studies would be valuable since this observation suggests that type of powder used may be more important than underlying reason for use.

The most obvious weakness in the argument for biologic credibility of the talc and ovarian cancer association is the lack of a clear dose response. Most talc and ovarian cancer studies that have addressed dose response, including this one, have failed to

demonstrate consistent dose response relationships with measures of the intensity of the exposure, especially when the trend is examined among users only. In attempting to address this weakness, we point out that it is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an “application of talc.” Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open. There is evidence from several studies that the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (Harlow *et al.*, 1992; Chang and Risch, 1997; Green *et al.*, 1997). We have also proposed that talc use during periods of ovulation may carry greater risk, based on the hypothesis that ovarian surface epithelial disruption and repair accompanying ovulation might allow talc to become entrapped within the inclusion cysts that form with ovulation.

Our current study also suggests that a term pregnancy may affect the relationship between talc and ovarian cancer in a manner that may be independent of ovulation. We observed that the association between talc and ovarian cancer was more apparent in women who used talc prior to a first liveborn pregnancy compared to those who used it only after a first liveborn pregnancy. This may suggest that ovarian tissue that has not (yet) gone through a pregnancy may be more susceptible to talc-induced damage than tissue that has undergone a pregnancy. A possible biologic explanation for this may involve an ovarian change, known as decidual reaction, that occurs during pregnancy. The decidual reaction refers to differentiation of stromal cells that occurs primarily in the endometrium of the pregnant uterus but which also may be seen in the fallopian tubes, pelvic peritoneum and ovarian surface (Herr *et al.*, 1978). Studies to determine whether the decidual reaction alters the susceptibility of ovaries (or pelvic peritoneum) to talc-induced damage may be informative.

Although we do not know precisely how use of talc in the genital area might induce ovarian cancer, some key elements supporting the biologic plausibility of the association have been established. It has been demonstrated that inert particles contaminating the vagina can reach the ovaries (Venter and Iturralde, 1979). Talc has been found in both normal and malignant ovarian tissue (Henderson *et al.*, 1979), although Heller *et al.* (1996) reported a poor correlation between the amount of talc in the ovaries and personal history of talc use. The patency of the female tract and the nature of ovarian cancer as a surface epithelial (mesothelial) lesion make the ovary a target for foreign body carcinogenesis. Indeed, human ovarian cancer has been demonstrated to be a consequence of occupational asbestos exposure (Keal, 1960). Talc, as a chemical relative of asbestos, appears able to induce histologic changes that are similar to those of asbestos, at least in the lungs (Kleinfeld *et al.*, 1967). Biologic credibility for an association would be strengthened by an animal model, but an experiment capturing all of the potential factors in the human "model" would be very difficult. These elements include chronicity of the exposure, anatomic and physi-

ologic uniqueness of women, effects of pregnancy and potential spread through coitus (as suggested by our finding related to ovarian cancer risk associated with a husband's use of talc). Rodent models seem poorly suited to address these issues because of their infrequent ovulation and the fact that the rodent ovary is encased in a bursal sac.

In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall or confounding. The dose-response relationship is weak but improved by considering factors such as closure of the female tract, ovulation and exposure prior to pregnancy, and we have outlined a plausible biologic rationale for this association. We estimate that avoidance of talc in genital hygiene might reduce the occurrence of a highly lethal form of cancer by at least 10%. Balanced against what are primarily aesthetic reasons for using talc in genital hygiene, the risk benefit decision is not complex. Appropriate warnings should be provided to women about the potential risks of regular use of talc in the genital area.

REFERENCES

- BOOTH, M., BERAL, V. and SMITH, P., Risk factors for ovarian cancer: a case-control study. *Brit. J. Cancer*, **60**, 592-598 (1989).
- CHANG, S. and RISCH, H., Perineal talc exposure and risk of ovarian carcinoma. *Cancer*, **79**, 2396-2401 (1997).
- CHEN, Y., WU, P.C., LANG, J.H., GE, W.Y., HARTGE, P. and BRINTON, L.A., Risk factors for epithelial ovarian cancer in Beijing, China. *Int. J. Epidemiol.*, **21**, 23-29 (1992).
- COOK, L.S., KAMB, M.L. and WEISS, N.S., Perineal powder exposure and the risk of ovarian cancer. *Amer. J. Epidemiol.*, **145**, 459-465 (1997).
- CRAMER, D.W., WELCH, W.R., SCULLY, R.E. and WOJCIECHOWSKI, C.A., Ovarian cancer and talc. *Cancer*, **50**, 372-376 (1982).
- GREEN, A., PURDIE, D., BAIN, C., SISKIND, V., RUSSELL, P., QUINN, M., WARD, B. and SURVEY OF WOMEN'S HEALTH STUDY GROUP, Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. *Int. J. Cancer*, **71**, 948-951 (1997).
- HARLOW, B.L., CRAMER, D.W., BELL, D.A. and WELCH, W.R., Perineal exposure to talc and ovarian cancer risk. *Obstet. Gynecol.*, **80**, 19-26 (1992).
- HARLOW, B.L. and WEISS, N.S., A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc. *Amer. J. Epidemiol.*, **130**, 390-394 (1989).
- HARTGE, P., HOOVER, R., LESHNER, L.P. and MCGOWAN, L., Talc and ovarian cancer (letter). *J. Amer. Med. Ass.*, **250**, 1844 (1983).
- HELLER, D.S., WESTHOFF, C., GORDON, R.E. and KATZ, N., The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Amer. J. Obstet. Gynecol.*, **174**, 1507-1510 (1996).
- HENDERSON, W., HAMILTON, T. and GRIFFITH, K., Talc in normal and malignant ovarian tissue. *Lancet*, **5**, 449 (1979).
- HERR, J.C., HEIDGER, P.M., SCOTT, J.R., ANDERSON, J.W., CURET, L.B. and MOSSMAN, H.W., Decidual cells in the human ovary at term I. Incidence, gross anatomy and ultrastructural features of merocrine secretion. *Amer. J. Anat.*, **152**, 7-28 (1978).
- KEAL, E.E., Asbestosis and abdominal neoplasms. *Lancet*, **2**: 1211-1216 (1960).
- KLEINFELD, MESSITE, J., KOOYMAN, O. and ZAKI, M.H., Mortality among talc miners and millers in New York State. *Arch. Environ. Health*, **14**, 663-667 (1967).
- PURDIE, D., GREEN, A., BAIN, C., SISKIND, V., WARD, B., HACKER, N., QUINN, M., WRIGHT, G., RUSSELL, P. and SUSIL, B., Reproductive and other factors and risk of epithelial ovarian cancer; an Australian case-control study. *Int. J. Cancer*, **6**, 678-684 (1995).
- ROSENBLATT, K.A., SZKLO, M. and ROSENSHEIN, N.B., Mineral fiber exposure and the development of ovarian cancer. *Gynecol. Oncol.*, **45**, 20-25 (1992).
- SHUSHAN, A., PALTIEL, O., ISCOVICH, J., ELCHALKAL, U., PERETZ, T. and SCHENKER, J.G., Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil. Steril.*, **65**, 13-18 (1996).
- TZONOU, A., POLYCHRONOPOULOU, A., HSIEH, C.C., REBELAKOS, A., KARAKATSANI, A. and TRICHOPOULOS, D., Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int. J. Cancer*, **55**, 508-510 (1993).
- VENTER, P.F. and ITURRALDE, M., Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *S. Afr. med J.*, **55**, 917-209 (1979).
- WHITTEMORE, A.S., WU, M.L., PAFFENBARGER, R.S., SARLES, D.L., KAMBERT, J.B., GROSSER, S., JUNG, D.L., BALLEEN, S. and HENDRICKSON, M., Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder tobacco, alcohol, and coffee. *Amer. J. Epidemiol.*, **128**, 1228-40 (1988).
- YOUNG, R.H., CLEMENT, P.B. and SCULLY, R.E., The Ovary (chapter 53). In Sternberg, S.S. (ed.), *Diagnostic Surgical Pathology* (2nd Ed.), p. 2213, Raven Press, New York (1994).

Exhibit 46

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TALC AND CARCINOMA OF THE OVARY AND CERVIX

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Summary

An extraction-replication technique was used to examine tissue from patients with ovarian and cervical tumours. In both conditions talc particles were found deeply embedded within the tumour tissue. The close association of talc to the asbestos group of minerals is of interest.

THE development in this laboratory of an extraction-replication technique (Henderson, 1969) for the study of foreign particles within tissues has allowed the *in situ* identification of crocidolite asbestos within the tissue of various mesotheliomas (Henderson *et al.*, 1969) removed from patients who had been concerned with the manipulation of asbestos in industry. This technique has now been applied to the study of tissue from ovarian and cervical carcinoma.

MATERIALS AND METHODS

Tissue

The tissue studied was obtained from patients with cancer of either the ovary or the cervix, and was first prepared as paraffin sections for normal routine histological examination but was unstained. Sections were then stained for histological assessment in the usual manner, and adjacent unstained tissue prepared for electron microscopy.

Replication Technique

The extraction-replication procedure has been described (Henderson, 1969). Sections of tissue were immersed in xylene and in ethanol, and the dehydrated tissue was then embedded by

immersing the section on to the surface of a thin sheet of acetone-softened cellulose acetate, mounted on a glass slide, and left to harden. On removing the slide, the embedded tissue was left in the cellulose acetate. The tissue was then outlined with thin strips of Scotch tape to form a shallow well, and a 10 per cent (v/v) polyvinyl alcohol (PVA) solution applied. When the PVA had hardened it was stripped from the section providing a replica of the tissue surface. Foreign particles associated with the tissue are often removed with the PVA during this stripping process.

A complete sequential examination through the embedded tissue is possible by taking successive strippings. These surface replicas were then preshadowed with platinum, a carbon film deposited for strength, and the PVA removed by floating the replica in a hot water bath. Replicas were mounted on electron microscope grids for examination, using the AEI-6B microscope.

RESULTS

No asbestos particles were found in any of the tissue studied. Particles of talc were identified in approximately 75 per cent (10 of 13) of the

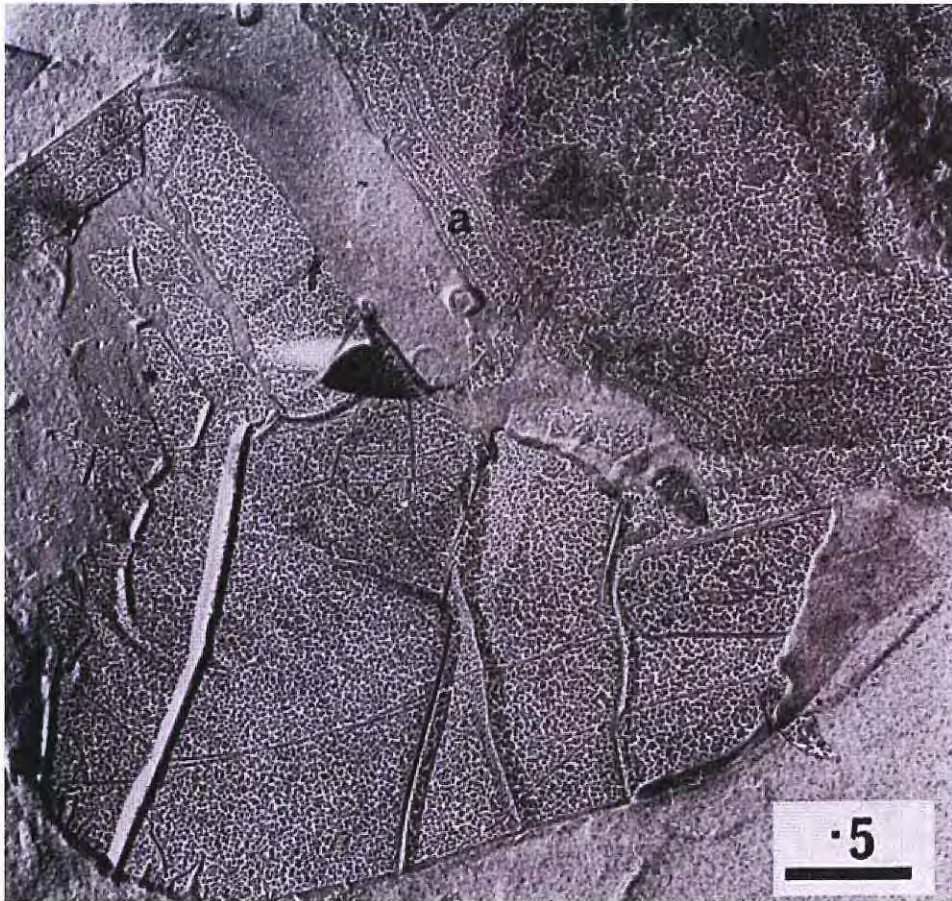


FIG. 1
Typical decoration pattern on a particle of natural talc. Numerous crystal lattice planes are shown (a). ($\times 30\,000$.)
Scale refers to $1.0\,\mu$.

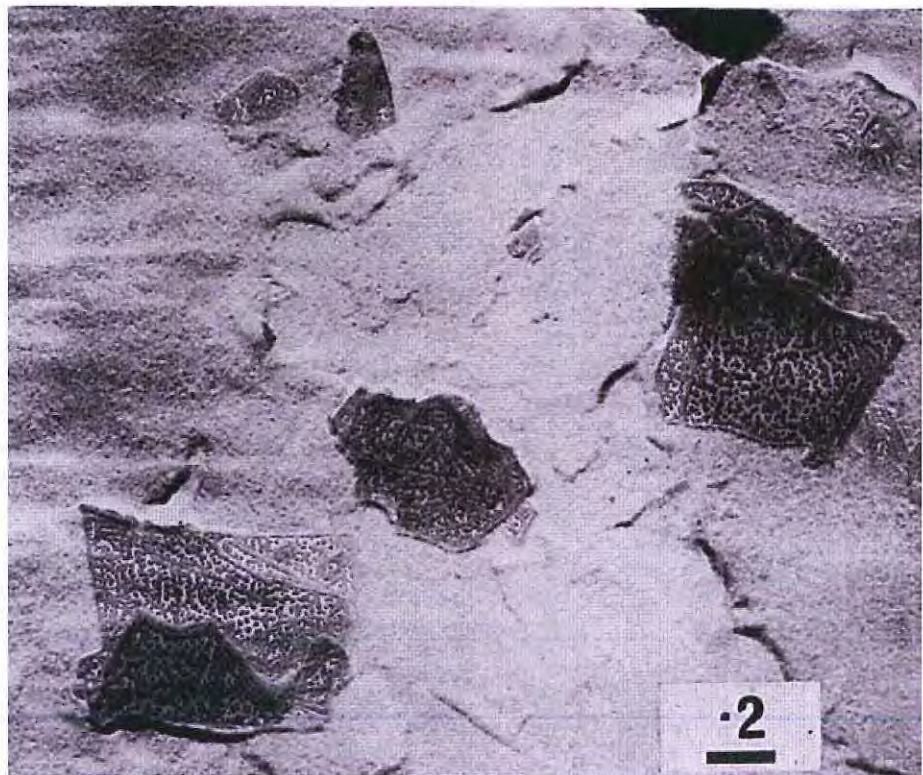


FIG. 2
Commercial talc preparations illustrating the decoration pattern. ($\times 40\,000$.)



FIG. 3

Micrograph of tissue from a serous papillary cystadenocarcinoma of the ovary removed from a 27-year-old female. No previous abdominal operations had been carried out. The decoration pattern and lattice planes are shown. ($\times 30\,000$.)

ovarian tumours. Using the replication technique identification of talc is possible because of the characteristic "decoration pattern" induced by the evaporation of platinum *in vacuo* on the crystal surface. Figure 1 shows this pattern on a particle of *natural* talc and the distinctive lattice planes of the crystals. Anthophyllite asbestos, which is known to be converted naturally to talc, is the only crystalline material which is at present indistinguishable from talc by using the replication technique. The decoration pattern on material from a commercial talc preparation is also demonstrated in Figure 2.

Material found within the ovarian tumours

and identified as talc is illustrated in Figure 3. The talc particles were found deep within the tumour tissue. Some were as small as 1000\AA in size but they were generally within a range from 1000\AA to $2\text{ }\mu$.

Talc particles were also found embedded within tumours of the cervix. Figure 4 shows one such particle embedded in a capillary wall within the tumour, and Figure 5 illustrates the decoration pattern of the particle at a higher magnification. Crystals as large as $5\text{ }\mu$. were found in tissue from the cervical tumours and were generally larger than those seen in the ovarian tumours. Talc crystals were found in

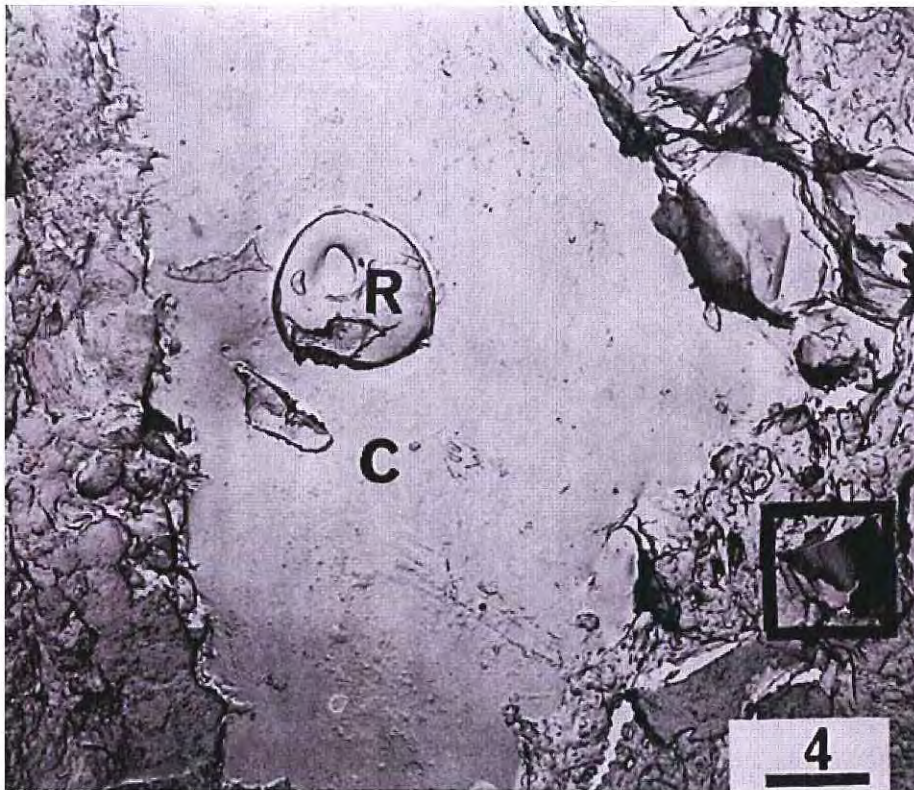


FIG. 4
Micrograph of tissue from
a squamous-cell carcinoma
of the cervix from a 62-
year-old female. C—capil-
lary, R—red cell. The
particle of talc can be seen
in the wall of the capillary.
($\times 3500$.)

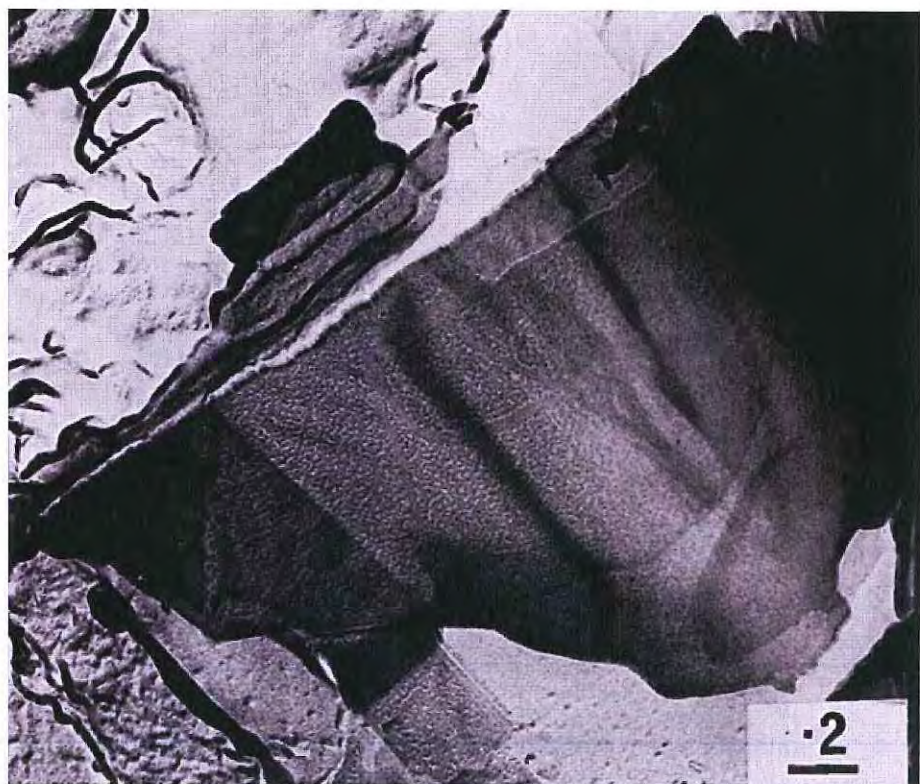


FIG. 5
A higher magnification of
the talc particles outlined in
Fig. 4. The typical decoration
pattern is shown. ($\times 40\,000$.)



FIG. 6
Talc particles found in
tissue from a pneumo-
coniotic lung. ($\times 30\,000$.)

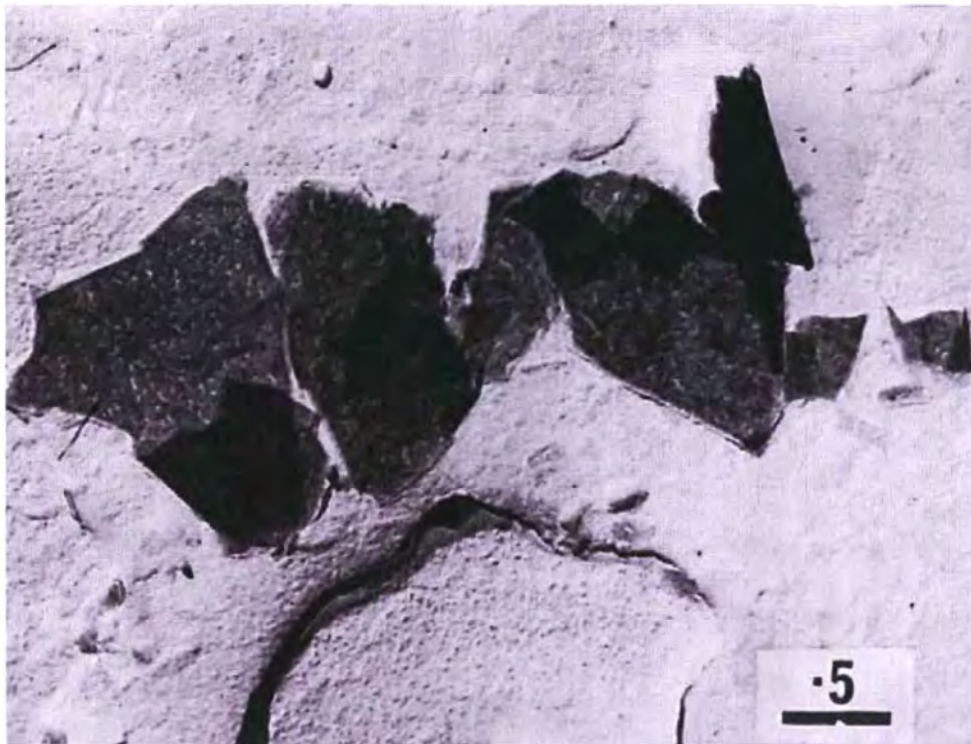


FIG. 7

Micrograph from the deepest part of an extensive papillary adenocarcinoma entirely replacing the endometrium in a 58-year-old woman, 8 years postmenopausal. Both ovaries were enlarged by hilar metastases, showing histological features similar to the primary endometrial lesion. Numerous talc particles were found in the primary endometrial carcinoma, but none in the metastatic ovarian tumours. ($\times 26\,000$.)

approximately 50 per cent of the cervical tumours examined (12 of 21) but it must be realized that these particles are extremely minute, often with the dimensions of viruses, and only small regions of the tumour tissue could be studied. Approximately ten replication "stripings" for electron-microscope examination are usually taken from each thin section of the tissue. Figure 6 illustrates the use of the technique in the examination of pneumoconiotic lung tissue from a patient whose industrial history indicated long exposure to Norwegian talc.

Many particles of talc were found concentrated in the deeper layers of a primary carcinoma of the endometrium (Fig. 7) whereas extensive studies of a secondary tumour in the ovary in the same patient did not show the presence of talc. Application of the technique to "normal" ovarian tissue removed from patients with breast cancer has also shown talc particles in 5 of 12 such tissues studied. Extensive study at high magnification with the electron microscope is, however, required for evaluation of a replica and particles could easily be missed.

The application of electron-microscope micro-analysis (EMMA-AEI, Harlow, England) to the particles extracted by the replication technique has provided preliminary evidence that the crystals contain magnesium and silicon, talc being a magnesium silicate.

DISCUSSION

The possibility that the increasing incidence of carcinoma in western society may be related to a corresponding increase in the use of asbestos (Graham and Graham, 1967) is of interest, especially with regard to pleural and peritoneal mesotheliomas in workers exposed to crocidolite asbestos in industry (Wagner *et al.*, 1960; Elwood and Cochrane, 1964). There have been a number of reports about the relationship between asbestos and carcinogenesis (Smith *et al.*, 1965; Jacob and Anspach, 1965). However, the identification of asbestos fibres within tissue is extremely difficult. Fine particles embedded within tumour tissue are usually beyond the limits of resolution of the optical microscope, and tissue incineration, followed by electron microscopy of the isolated particles, may be unreliable if chemical changes are

induced by the procedure. Using normal light microscopy, identification of asbestos particles is based on the presence of characteristic ferritin bodies on some of the fibres, although these cannot easily be distinguished from similar bodies around elastin fibres (Henderson *et al.*, 1970). This procedure may not, however, be as unreliable as the use of polarized light for the demonstration of brightly illuminated "birefringent crystals of asbestos".

The replication technique (Henderson, 1969) failed to show asbestos fibres in the ovarian neoplasms studied. On the other hand, there was good evidence for the presence of talc, often indistinguishable from anthophyllite asbestos, within the ovarian tissue. (Anthophyllite is converted naturally to talc.) The talc particles were found localized deep within tumour tissues, and not universally dispersed throughout the tumour. The talc particles in the ovary were generally much smaller than those found in the tissue from the tumours of the cervix.

The relationship between asbestos and mesotheliomas appears well established, and the replication technique has provided unequivocal evidence for the presence of fibres within such tumours. This technique has also produced evidence for the presence of talc in tissue from pneumoconiotic lungs of a patient with an industrial history of exposure to Norwegian talc (Henderson *et al.*, 1970). The presence of mica, kaolin and asbestos fibres were also identified in tissue from these pneumoconiotic lung tissue.

Although it is impossible to incriminate talc as a primary cause of carcinomatous changes within either the cervix or the ovary on the preliminary observations described here, the possibility that talc may be related to other predisposing factors should not be disregarded and further investigations are obviously required.

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REFERENCES

- Elwood, P. C., and Cochrane, A. L. (1964): *British Journal of Industrial Medicine*, 21, 304.
- Graham, J., and Graham, R. (1967): *Environmental Research*, 1, 115.
- Henderson, W. J. (1969): *Journal of Microscopy*, 89, 369.
- Henderson, W. J., Gough, J., and Harse, J. (1970): *Journal of Clinical Pathology*, 23, 104.
- Henderson, W. J., Harse, J., and Griffiths, K. (1969): *European Journal of Cancer*, 5, 621.
- Jacob, G., and Anspach, M. (1965): *Annals of New York Academy of Sciences*, 132, 536.
- Keal, E. E. (1960): *Lancet*, 2, 1211.
- Smith, W. E., Miller, L., Elsasser, R. E., and Hubert, D. D. (1965): *Annals of New York Academy of Sciences*, 132, 456.
- Wagner, J. C., Sleggs, C. A., and Marchand, P. (1960): *British Journal of Industrial Medicine*, 12, 260.

Exhibit 47

The relationship between perineal cosmetic talc usage and ovarian talc particle burden

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OBJECTIVE: Epidemiologic studies support the hypothesis of a dose-related risk of epithelial ovarian cancer with perineal talc exposure. Frequency and duration of talc usage has not been previously correlated with ovarian talc content.

STUDY DESIGN: Ovaries were studied from 24 women undergoing incidental oophorectomy who were interviewed regarding talc usage. Twelve subjects reported frequent perineal talc applications; the twelve controls reported no use. Ovarian tissue blocks were digested and analyzed by polarized light microscopy and analytic electron microscopy to identify and quantify talc.

RESULTS: Talc was identified in all 24 cases by either light or electron microscopy. Talc particle counts were completely unrelated to reported levels of perineal talc exposure.

CONCLUSIONS: The detection of talc in all ovaries demonstrates that it can reach the upper genital tract. Widespread exposure to talc during diapering may contribute to the ubiquitous presence of talc in ovarian tissue. (AM J OBSTET GYNECOL 1996;174:1507-10.)

Key words: Talc, ovary

Epidemiologic evidence suggests that perineal exposure to talc is associated with an increased risk of epithelial ovarian cancer in a dose-related fashion.^{1,5} Other epidemiologic studies have shown no increased risk of ovarian cancer associated with talc.^{6, 7} Studies show access of particulate matter into the female peritoneal cavity through the transvaginal route.⁸⁻¹⁰ A few reports have identified talc in ovarian tissue,^{11, 12} both benign and malignant, but these data were not correlated with an exposure history. Other potential genital tract exposures in a woman's life include surgical gloves,¹³ condoms, and diaphragms. Diapering with talc during infancy is another potential exposure. Epidemiologic studies have not linked these exposures to an increased risk of ovarian cancer.^{1, 2}

If transvaginal transport of perineally applied talc occurs, women with the heaviest exposures may show the largest talc particle burdens in their ovaries. Tissue digestion techniques are an accepted analytic adjunct in the identification and quantification of asbestos in the lungs of occupationally exposed individuals^{14, 15} and are useful in the identification and quantification of talc as well.

The goal of this pathoepidemiologic study was to correlate the history of perineal talc usage with the talc particle burden found in the ovaries.

Material and methods

In a case control study of benign ovarian neoplasms at Columbia Presbyterian Medical Center, women undergoing surgery from 1992 to 1993 were interviewed regarding various factors, including talc usage. Subjects were also questioned regarding possible occupational exposures to asbestos, and mothers were contacted regarding diapering history whenever feasible.

Subjects were categorized for talc exposures as follows. Women who reported no direct application of talc to the perineum or to underwear were considered unexposed. For women who reported talc application to underwear or the perineum, the total number of lifetime applications was estimated as the average frequency of use times the number of years of use. For instance, a woman who reported perineal talc application twice per day for 10 years was considered to have 7240 applications. To simplify the classification of exposed and unexposed women, subjects who reported tubal ligation, diaphragm use, or feminine hygiene spray use were excluded from this analysis.

Interviewed subjects from the parent case control study who had a normal contralateral ovary in the surgical specimen were eligible for this substudy. Sections of normal ovary from the 12 women who reported the largest number of perineal talc applications were analyzed. For each of these subjects the unexposed woman closest in age was selected as a control. In addition, the ovaries of two stillborn fetuses were analyzed as negative controls.

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Table I. Talc particle counts in women who reported perineal cosmetic talc usage

Subject No.	age (yr)	Lifetime talc applications*	EM talc particle counts†	Polarized light microscopic counts†	Asbestos detected	Talc use with diapering
1	49	4,784	1,600,288	96	No	Yes
2	49	5,475	0	54	No	Unknown
3	57	6,552	0	100	Yes	No
4	31	8,144	0	114	No	Unknown
5	43	10,556	0	464	Yes	Unknown
6	45	11,284	151,300	300	No	Yes
7	50	11,648	236,406	345	No	Yes
8	57	15,600	0	75	No	Yes
9	66	18,980	0	250	Yes	Yes
10	47	21,840	1,576,000	111	No	Unknown
11	44	23,660	0	348	No	Yes
12	44	39,312	7,565,000	26	Yes	Unknown

EM, Electron microscopy.

*Frequency of use × Years of use.

†Per gram wet tissue weight.

Ovarian tissue in blocks was deparaffinized, rehydrated, blotted dry, and weighed. Digestion with 5% potassium hydroxide was performed at 70° C for 2 to 4 hours. After complete digestion, the tissue was centrifuged at 12,000 revolutions/min for 20 minutes. The potassium hydroxide was removed, leaving a pellet to which approximately 20 ml of distilled water was added. The pellet was resuspended by use of a microultrasonic cell disrupter at 50 W for 5 seconds. Centrifugation, distilled water wash, and microultrasonic cell disrupter were repeated three times. The distilled water was removed, and the pellet was resuspended in 5 to 10 ml of distilled water. Drops of 10 μ l of the final suspension were placed on nickel formvar and carbon-coated locator grids and air-dried. Transmission electron microscopy to identify particles and their size was performed. The identity of the particles was determined by energy-dispersive spectroscopy and confirmed by electron diffraction. Grids were viewed at both 10,000 and 19,000 diameters. All talc particles observed were counted. Cytospin slides for polarized light microscopy were prepared from the same final suspension as the electron microscopy grids. Polarized light microscopy counted larger talc particles (limits of detection approximately 1 μ m), whereas electron microscopy detected smaller ones (limits of detection approximately 0.5 nm).

Routinely, all solutions are checked for detectable limits of contaminating particles; all places where particles could have contaminated the specimen, such as paraffin, are also controlled for.

Associations between talc exposure and talc particle count in the 12 exposed subjects were assessed with Spearman's rank correlation coefficient.

Results

Detailed results can be seen in Tables I and II. The mean age of the patients was 49 years (range 29 to 66

years). For eight exposed subjects, a control was found who was within 4 years of her age. Talc particle counts were not related to age in either the exposed or unexposed subjects ($p > 0.25$). The mean number of lifetime exposures for the women reporting perineal talc use was 14,820 (range 4784 to 39,312). Talc was detected in all ovaries by either polarized light or electron microscopy. There was a wide range of values, as shown by the large SDs. Table III shows that talc particles were observed to a similar extent with both exposed and unexposed subjects.

Neither the light microscopic nor electron microscopic values correlated with reported perineal talc usage (p values 0.37 and 0.45). There was a negative correlation between the values obtained by light microscopy and electron microscopy ($r = -0.34$, $p = 0.05$). An attempt to contact mothers of subjects was successful for 11 of the 24 subjects. Ten of these reported using talc to diaper their babies, which indicates that lifetime talc exposure may be underestimated for nearly all the subjects. Analyses of two fetal ovaries and a pair of surgical gloves was completely negative for talc.

In one subject we studied both ovaries; on the right side we detected no talc by electron microscopy and 556 particles by light microscopy, and on the left side we detected 1,669,000 particles per gram of wet weight by electron microscopy and 6 particles by light microscopy. Hematoxylin-eosin stained slides from the analyzed sections of tissue were examined. There was no evidence of response to talc, such as foreign body giant cell reactions or fibrosis in the tissue. Asbestos was detected in ovaries of five of the subjects with no talc exposure and in four ovaries of the talc-exposed subjects.

Comment

If transvaginal transport of perineally applied talc occurs, we would expect women with the heaviest exposures to show the largest talc particle burden in their ovaries.

Table II. Talc particle counts in women without history of perineal cosmetic talc usage

Subject No.	Age (yr)	Reported exposure history	EM talc particle count*	Polarized light microscopic talc particle counts*	Asbestos detected	Talc use with diapering
1	63	0	1,350,000	89	No	Yes
2	57	0	315,250	111	No	Yes
3	29	0	0	42	No	Unknown
4	48	0	1,669,000	6	Yes	Unknown
5	59	0	315,208	166	Yes	Yes
6	40	0	0	69	Yes	Yes
7	43	0	0	566	Yes	Unknown
8	64	0	0	420	Yes	Yes
9	49	0	0	53	No	Unknown
10	54	0	0	1139	No	Unknown
11	32	0	63,042	2200	No	Unknown
12	58	0	472,813	0	No	Unknown

EM, Electron microscopy.

*Per gram wet tissue weight.

Table III. Comparison of particle burdens between reported exposed and nonexposed subjects

Talc exposure	No. of subjects with talc by EM	No. of subjects with talc by light microscopy	Mean EM particle count*	SD	Mean light microscopic particle count*	SD
Reported talc use (n = 12)	5/12	12/12	927,416	2,174,888	190	144
No reported talc use (n = 12)	6/12	11/12	348,776	570,055	405	655

EM, Electron microscopy.

*Per gram wet tissue weight.

Tissue digestion techniques have been used to identify and quantify particle burdens of various organic materials in human tissue. The most notable use of this technique is in the identification of asbestos in the lungs of occupationally exposed individuals.^{14, 15} Other studies have examined other organs as well. In the 1979 report of Henderson et al.¹¹ ovaries were studied after an oxygen incineration procedure. They found 6900 to 55,100 talc particles per gram of wet weight in three normal ovaries, 17,400 to 24,300 in three cystic ovaries, and 6400 to 24,500 in three ovarian adenocarcinomas. No exposure histories were stated.

Our study attempted to correlate ovarian talc particle burden with exposure history. Our results do not support a linear dose-related ovarian talc particle burden. However, the mean electron microscopic particle count was much higher in talc users. Perhaps perineal talc does contribute to the ovarian particle burden; however, factors other than dosage may contribute. Other factors to consider include method of application, type of talc, and the possible contribution of inhaled talc particles. The range of talc particle values obtained in this study was wide, as evidenced by the large SDs. This spread of values was also present in the study of Henderson et al.¹¹ and in much of the asbestos fiber burden literature. Talc may be unevenly distributed throughout the ovarian paren-

chyma. This is supported by the discrepant counts we obtained on the one subject who had analysis of both ovaries. The lack of correspondence between polarized light and electron microscopy counts was due to measurement of different size particles.

Undocumented exposures to talc may partly explain the lack of correlation between adult histories of perineal cosmetic talc applications and ovarian burdens. Although both examination and surgical gloves in the past were dusted with talc, we cannot document this exposure. The gloves we currently use are talc free, according to the company and to our analyses. Ten of the 11 available mothers reported using talc while diapering their babies; this ubiquitous exposure may also contribute to the ovarian particle burdens.

Talc as a possible etiologic agent in the development of epithelial ovarian cancer may be related to asbestos exposure in several ways. Aside from the chemical similarities between the two, many cosmetic talcs contained significant amounts of asbestos, particularly before 1976.¹ Although tremolite asbestos has been documented as a contaminant of some talc preparations, the types of asbestos detected here are more commonly associated with an environmental (chrysotile) or occupational (chrysotile and crocidolite) exposure.¹⁶

The detection of talc in all the ovaries demonstrates

that talc can reach the upper genital tract. However, the quantity detected in this study did not correlate well with the reported exposure. Further study is required to elucidate whether the presence of talc in ovarian tissue is pathogenic.

REFERENCES

1. Cramer D, Welch W, Scully RE. Ovarian cancer and talc: a case control study. *Cancer* 1982;50:372-6.
2. Harlow B, Cramer D, Bell D, Welch W. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* 1992;80:19-26.
3. Harlow B, Weiss N. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol* 1989;130:390-4.
4. Longo D, Young R. Cosmetic talc and ovarian cancer. *Lancet* 1979;2:349-51.
5. Scully RE. Ovarian tumors—a review. *Am J Pathol* 1977;87:686-720.
6. Hartge P, Stewart P. Occupation and ovarian cancer: a case-control study in the Washington DC metropolitan area 1978-81. *J Occup Med* 1994;36:924-7.
7. Tzonou A, Polychronopoulou A, Hsieh CC, et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer* 1993;55:408-10.
8. Egli G, Newton M. The transport of carbon particles in the human female reproductive tract. *Fertil Steril* 1961;2:151-5.
9. Henderson W, Hamilton T, Baylis M, Pierrepont CG, Griffiths K. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. *Environ Res* 1986;40:247-50.
10. Scully RE. Atlas of tumor pathology, second series, fascicle 16: tumors of the ovary and maldeveloped gonads. Washington, DC: Armed Forces Institute of Pathology, 1979.
11. Henderson W, Hamilton T, Griffiths K. Talc in normal and malignant ovarian tissue. *Lancet* 1979;5:499.
12. Henderson W, Joslin C, Turnbull A, Griffiths K. Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonw* 1971;78:266-72.
13. Henderson W, Melville-Jones C, Barr W, Griffiths K. Identification of talc on surgeons' gloves and in tissue for starch granulomas. *Br J Surg* 1975;62:941-4.
14. Heller D, Gordon R. Demonstration of asbestos fibers in a ten year old sputum sample. *Am J Ind Med* 1991;20:415-9.
15. Roggli V, Pratt P. Number of asbestos bodies on iron-stained tissue sections in relation to asbestos body counts in lung tissue digests. *Hum Pathol* 1983;14:355-61.
16. Heller D, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. *Am J Ind Med* (in press).